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(54) **Detection methods using TIMP 1 for colon cancer diagnosis**

(57) The present invention relates to a method for detecting the presence of colorectal cancer in an individual, wherein colorectal cancer is detected by detecting the presence of Reg1 $\alpha$  or TIMP1 nucleic acid or amino acid molecules in a clinical sample obtained from the patient, wherein Reg1 $\alpha$  or TIMP1 expression is indicative of the presence of colorectal cancer. The invention further relates to a method for detecting the presence of

colorectal cancer in an individual, wherein colorectal cancer is detected by detecting the presence of Reg1 $\alpha$  or TIMP1 nucleic acid or amino acid molecules in a clinical sample, in addition to detecting the presence of one or more additional colorectal cancer associated markers.

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## Description

5 [0001] Colorectal carcinoma is a malignant neoplastic disease. There is a high incidence of colorectal carcinoma in the Western world, particularly in the United States. Tumors of this type often metastasize through lymphatic and vascular channels. Many patients with colorectal carcinoma eventually die from this disease. In fact, it is estimated that 62,000 persons in the United States alone die of colorectal carcinoma annually.

10 [0002] However, if diagnosed early, colorectal cancer may be treated effectively by surgical removal of the cancerous tissue. Colorectal cancers originate in the colorectal epithelium and typically are not extensively vascularized (and therefore not invasive) during the early stages of development. Colorectal cancer is thought to result from the clonal expansion of a single mutant cell in the epithelial lining of the colon or rectum. The transition to a highly vascularized, invasive and ultimately metastatic cancer which spreads throughout the body commonly takes ten years or longer. If the cancer is detected prior to invasion, surgical removal of the cancerous tissue is an effective cure. However, colorectal cancer is often detected only upon manifestation of clinical symptoms, such as pain and black tarry stool. Generally, such symptoms are present only when the disease is well established, often after metastasis has occurred, and the prognosis for the patient is poor, even after surgical resection of the cancerous tissue. Early detection of colorectal cancer therefore is important in that detection may significantly reduce its morbidity.

15 [0003] Invasive diagnostic methods such as endoscopic examination allow for direct visual identification, removal, and biopsy of potentially cancerous growths such as polyps. Endoscopy is expensive, uncomfortable, inherently risky, and therefore not a practical tool for screening populations to identify those with colorectal cancer. Non-invasive analysis of stool samples for characteristics indicative of the presence of colorectal cancer or precancer is a preferred alternative for early diagnosis, but no known diagnostic method is available which reliably achieves this goal. A reliable, non-invasive, and accurate technique for diagnosing colorectal cancer at an early stage would help save many lives.

20 [0004] Ectopic expression of the pancreatic regenerating gene (RegI) has been identified previously in colorectal tumors, and suggested as a potential marker for colorectal cancer (Zenilman et al., (1997) *J. Gastrointest. Surg.*, 1: 194; Watanabe et al., (1990) *J. Biol. Chem.*, 265: 7432; Birse and Rosen, WO01/12781). At present, there is no reliable method known to those of skill in the art for the rapid and accurate detection of Reg1 $\alpha$  in the serum of colorectal cancer patients (Satomura et al., (1995) *J. Gastroenterol.* 30: 643). There is thus a need in the art for a method of detecting, and/or monitoring colorectal cancer in a patient utilizing the expression of Reg1 $\alpha$  in serum.

25 [0005] The present invention provides a method of detecting, monitoring or determining the therapeutic response of colorectal cancer in an individual as well as compositions, and kits for performing the method. In its most general aspect, the method comprises: obtaining a clinical sample from the individual and detecting the presence of one or more of the nucleic acid sequences of SEQ ID Nos. 1, 3, or 5-71, or the amino acid sequences of SEQ ID Nos. 2, 4, or 72-138.

30 [0006] The invention also provides a method of detecting, monitoring or determining the therapeutic response of colorectal cancer in an individual as well as compositions, and kits for performing the method, which, in its preferred aspect, comprises: obtaining a clinical sample from the individual and detecting the presence of Reg1 $\alpha$  or TIMP1 in said sample, wherein the presence of Reg1 $\alpha$  or TIMP1 in the sample is indicative of the presence or stage of colorectal cancer in the individual.

35 [0007] In one embodiment, the step of detecting comprises: contacting said clinical sample with a ligand which is capable of binding to Reg1 $\alpha$  or TIMP1 under conditions which permit the ligand to bind to Reg1 $\alpha$  or TIMP1; and detecting the binding of the ligand to Reg1 $\alpha$  or TIMP1, wherein detection of binding is indicative of the presence of Reg1 $\alpha$  or TIMP1 in the sample. The polypeptide ligand may comprise, for example, an antibody, peptide, oligonucleotide, or other molecule that specifically binds Reg1 $\alpha$  or TIMP1. In a currently preferred embodiment, the clinical sample comprises serum.

40 [0008] The present invention further provides a method of detecting, monitoring, or determining the presence of colorectal cancer in an individual comprising: obtaining a clinical sample from said individual; and detecting the presence of Reg1 $\alpha$  or TIMP1 and at least one other colorectal cancer associated marker in the sample, wherein the presence of Reg1 $\alpha$  or TIMP1 and the at least one other colorectal cancer associated marker is indicative of colorectal cancer in the individual. The colorectal cancer associated marker may comprise, for example, one or more of the nucleic acid sequences of SEQ ID Nos 1, 3, or 5-71, or the amino acid sequences of SEQ ID Nos 2, 4, or 72-138, or derivatives or homologs thereof having substantially the same binding specificity.

45 [0009] In a preferred embodiment, the above step of detecting comprises contacting a serum sample with a first ligand which is capable of binding to Reg1 $\alpha$  or TIMP1 and a second ligand which is capable of binding to the colorectal cancer associated marker, under conditions which permit the first and second ligands to bind to Reg1 $\alpha$  or TIMP1 and the colorectal cancer associated marker, respectively; and detecting the binding of the first ligand to Reg1 $\alpha$  or TIMP1 and the second ligand to the colorectal cancer associated marker, wherein detection of binding is indicative of the presence of Reg1 $\alpha$  or TIMP1 and the colorectal cancer associated marker in said sample. The polypeptide ligand may comprise, for example, an antibody, peptide, oligonucleotide, or other molecule that specifically binds

Reg1 $\alpha$  or TIMP1.

**[0010]** The present invention also provides a method of detecting, monitoring or determining the presence of colorectal cancer in an individual comprising: obtaining a clinical sample from an individual; and detecting the presence of a nucleic acid molecule which encodes Reg1 $\alpha$  or TIMP 1 in said sample, wherein the presence of the nucleic acid molecule in the sample is indicative of colorectal cancer in the individual.

**[0011]** The invention still further provides a method of detecting, monitoring or determining the presence of colorectal cancer in an individual comprising: obtaining a clinical sample from an individual; and detecting the presence of a nucleic acid molecule which encodes Reg1 $\alpha$  or TIMP1 and at least one other nucleic acid molecule which encodes at least one other colorectal cancer associated marker in the sample, wherein the presence of the nucleic acid sequence encoding Reg1 $\alpha$  or TIMP1 and the nucleic acid sequence encoding the at least one other colorectal cancer associated marker is indicative of colorectal cancer in the individual. In a preferred embodiment, the colorectal cancer associated marker is one or more of the nucleic acid sequences of SEQ ID Nos 1, 3, or 5-71, or the amino acid sequences of SEQ ID Nos 2, 4, or 72-138, or derivatives or homologs thereof having substantially the same binding specificity.

**[0012]** Figure 1 shows the level of Reg1 $\alpha$  polypeptide present in serum obtained from normal control patients (n=35), patients diagnosed with inflammatory bowel disease (IBD; n=7), patients diagnosed with cirrhosis (n=7), and patients diagnosed with colorectal cancer (n=63).

**[0013]** Figure 2 shows the level of Reg1 $\alpha$  polypeptide measured in the colorectal cancer patient group (n=63) differentiated based on cancer severity. The degree of cancer has been established by Dukes'-type staging, and data from patients with Dukes'-type A, B, C, and D is shown.

**[0014]** Figure 3 shows a graphical representation of the plasma level of TIMP 1 polypeptides, along with one or more other colorectal cancer associated markers obtained from patients with colorectal cancer.

**[0015]** The present invention is based, in part, on the discovery that the expression of the human islet regenerating protein, Reg1 $\alpha$ , is increased in patients with colorectal cancer, and as such is a valuable marker for the identification of colorectal cancer in humans. The present invention further provides for the early detection of colorectal cancer by detecting the presence of Reg1 $\alpha$  or TIMP1 (and optionally, one or more additional colorectal cancer associated markers) in a clinical sample from an individual. The invention provides further, the ability to monitor the recurrence of colorectal cancer in a patient wherein colorectal cancer has been previously detected, by monitoring the levels of Reg1 $\alpha$  or TIMP1 polypeptide or polynucleotide sequences present in a clinical sample from the patient, wherein an increase in Reg1 $\alpha$  or TIMP1 in the sample is indicative of the recurrence of colorectal cancer. The invention provides still further, the ability to monitor the decrease in colorectal cancer in response to a therapeutic agent, whereby the levels of Reg1 $\alpha$  or TIMP1 are measured in a clinical sample obtained from a patient who has received therapeutic treatment for colorectal cancer, wherein a decrease in the levels of Reg1 $\alpha$  or TIMP1 detected in the clinical sample from the patient is indicative of the efficacy of the therapeutic treatment. In any of the preceding embodiments, Reg1 $\alpha$  or TIMP1 polynucleotide or polypeptide expression levels are measured in concert with at least one additional colorectal cancer associated marker.

**[0016]** Accordingly, the present invention relates in part to novel methods for identifying cancer in an individual, particularly colorectal cancer, by screening for genes or gene products, which are over or underexpressed in cancer relative to the level of expression in normal tissue, such as colon tissue. Alternatively, the invention provides a method for the identification of cancer in an individual by screening for genes or gene products which are over- or underexpressed in colorectal cancer, and which are detectable in a clinical sample of an individual with colorectal cancer.

**[0017]** In a preferred embodiment, the present invention relates to methods useful for the detection of colorectal cancer in an individual, preferably a human patient by detecting serum levels of Reg1 $\alpha$  or TIMP1. The invention relates to methods for colorectal cancer detection that utilize either or both techniques of detecting the presence of the Reg1 $\alpha$  or TIMP1 gene or detecting the Reg1 $\alpha$  or TIMP1 encoded polypeptide product in the serum of an individual, or alternatively in a clinical sample from an individual.

**[0018]** The present invention further provides methods for the identification of colorectal cancer wherein cancer is detected by the identification of Reg1 $\alpha$  or TIMP1 expression in a patient clinical sample, in combination with the expression in the same sample of at least one other colorectal cancer associated marker. This combination of Reg1 $\alpha$  or TIMP1 detection analysis, in concert with the detection of additional colon-cancer markers provides an efficient and reliable method for detecting the presence of colorectal cancer.

**[0019]** The methods described herein which specifically refer to the detection of Reg1 $\alpha$ , may equally be applied to the detection of TIMP1 by one of skill in the art, based on the disclosure of the present specification:

**[0020]** As used herein, "Reg1 $\alpha$ " refers to a polypeptide molecule having the sequence of either of SEQ ID Nos 2 or 4. Reg1 $\alpha$  as used herein, also refers to a polypeptide which is encoded by either of the sequences of SEQ ID Nos. 1 or 3. The sequences of SEQ ID Nos 2 and 4 each represent a functional Reg1 $\alpha$  protein, but differ from each other by four amino acids in the leader sequence which is cleaved off during protein synthesis.

**[0021]** As used herein, "TIMP 1" refers to a polypeptide molecule having the sequence of SEQ ID NO: 100. TIMP1 as used herein, also refers to a nucleotide which is encoded by the sequence of SEQ ID NO: 33, or a functional homolog

thereof.

**[0022]** As used herein, a "clinical sample" refers to a tissue, cellular, or fluid sample obtained from an individual. A "clinical sample", as used herein, can refer to a cells, circulating cells (e.g., circulating cells in blood), cells obtained from specific anatomical locations, or specific cell types (e.g., colon cell, gastrointestinal cell, cancerous cell, etc.), a tissue sample, or physiological fluids such as lymph, bile, serum, plasma, urine, synovial fluid, blood, CSF, mucus membrane secretions, or other physiological samples such as stool. Preferably, the clinical sample is serum or plasma. A colorectal cancer associated marker of the invention, such as TIMP1, may be detected in a suitable "clinical sample" where the suitability of a particular type of clinical sample for the detection of a specific colorectal cancer associated marker may be readily determined by one of skill in the art.

**[0023]** As used herein, "detecting" refers to the identification of the presence or absence of a molecule in a sample. Where the molecule to be detected is a polypeptide, the step of detecting can be performed by binding the polypeptide with an antibody that is detectably labeled. A detectable label is a molecule which is capable of generating, either independently, or in response to a stimulus, an observable signal. A detectable label can be, but is not limited to a fluorescent label, a chromogenic label, a luminescent label, or a radioactive label. Methods for "detecting" a label include quantitative and qualitative methods adapted for standard or confocal microscopy, FACS analysis, and those adapted for high throughput methods involving multiwell plates, arrays or microarrays. One of skill in the art can select appropriate filter sets and excitation energy sources for the detection of fluorescent emission from a given fluorescent polypeptide or dye. "Detecting" as used herein can also include the use of multiple antibodies to a polypeptide to be detected, wherein the multiple antibodies bind to different epitopes on the polypeptide to be detected. Antibodies used in this manner can employ two or more detectable labels, and can include, for example a FRET pair. A polypeptide molecule, such as Reg1 $\alpha$ , is "detected" according to the present invention when the level of detectable signal is at all greater than the background level of the detectable label, or where the level of measured nucleic acid is at all greater than the level measured in a control sample.

**[0024]** As used herein, "detecting" as it refers to detecting the presence of a target nucleic acid molecule (e.g., a nucleic acid molecule encoding Reg1 $\alpha$ , or other colorectal cancer-specific sequence) refers to a process wherein the signal generated by a directly or indirectly labeled probe nucleic acid molecule (capable of hybridizing to a target, e.g., a sequence encoding Reg1 $\alpha$ , in a serum sample) is measured or observed. Thus, detection of the probe nucleic acid is directly indicative of the presence, and thus the detection, of a target nucleic acid, such as a sequence encoding Reg1 $\alpha$ . For example, if the detectable label is a fluorescent label, the target nucleic acid (e.g., the nucleic acid molecule encoding Reg1 $\alpha$ ) is "detected" by observing or measuring the light emitted by the fluorescent label on the probe nucleic acid when it is excited by the appropriate wavelength, or if the detectable label is a fluorescence/quencher pair, the target nucleic acid is "detected" by observing or measuring the light emitted upon association or dissociation of the fluorescence/quencher pair present on the probe nucleic acid, wherein detection of the probe nucleic acid indicates detection of the target nucleic acid. If the detectable label is a radioactive label, the target nucleic acid, following hybridization with a radioactively labeled probe is "detected" by, for example, autoradiography. Methods and techniques for "detecting" fluorescent, radioactive, and other chemical labels may be found in Ausubel et al. (1995, Short Protocols in Molecular Biology, 3<sup>rd</sup> Ed. John Wiley and Sons, Inc.). Alternatively, a nucleic acid may be "indirectly detected" wherein a moiety is attached to a probe nucleic acid which will hybridize with the target, such as an enzyme activity, allowing detection in the presence of an appropriate substrate, or a specific antigen or other marker allowing detection by addition of an antibody or other specific indicator. Alternatively, a target nucleic acid molecule can be detected by amplifying a nucleic acid sample prepared from a patient clinical sample, using oligonucleotide primers which are specifically designed to hybridize with a portion of the target nucleic acid sequence. Quantative amplification methods, such as, but not limited to TaqMan, may also be used to "detect" a target nucleic acid according to the invention. A nucleic acid molecule is "detected" as used herein where the level of nucleic acid measured (such as by quantitative PCR), or the level of detectable signal provided by the detectable label is at all above the background level.

**[0025]** As used herein, "detecting" refers further to the early detection of colorectal cancer in a patient, wherein "early" detection refers to the detection of colorectal cancer at Dukes stage A or preferably, prior to a time when the colorectal cancer is morphologically able to be classified in a particular Dukes stage. "Detecting" as used herein further refers to the detection of colorectal cancer recurrence in an individual, using the same detection criteria as indicated above. "Detecting" as used herein still further refers to the measuring of a change in the degree of colorectal cancer before and/or after treatment with a therapeutic agent. In this case, a change in the degree of colorectal cancer in response to a therapeutic agent refers to an increase or decrease in the expression of Reg1 $\alpha$  (and optionally, one or more additional colorectal cancer associated markers), or alternatively, in the amount of Reg1 $\alpha$  polypeptide (and optionally, one or more additional colorectal cancer associated markers) present in a clinical sample by at least 10% in response to the presence of a therapeutic agent relative to the expression level in the absence of the therapeutic agent.

**[0026]** As used herein, "individual" refers to a mammal, preferably a human.

**[0027]** As used herein, a "ligand" refers to a molecule which is capable of binding a polypeptide. A "polypeptide ligand" useful in the present invention includes, but is not limited to an antibody, a monoclonal antibody, a polyclonal



antibody, an antibody fragment (e.g., Fv, scFv, or Fab), a small molecule, or a nucleic acid aptamer. A "ligand" as used herein can also refer to a "nucleic acid ligand", such as an oligonucleotide, polynucleotide, DNA, RNA, mRNA, or cDNA, which is capable of binding to a complementary nucleic acid molecule, or polypeptide molecule.

**[0028]** The term "antibody" as used herein is intended to include whole antibodies, e.g., of any isotype (IgG, IgA, IgM, IgE, etc), and includes fragments thereof, and single-chain antibodies, which also are specifically reactive with a vertebrate, e.g., mammalian, protein. Antibodies can be fragmented using conventional techniques and the fragments screened for utility in the same manner as described above for whole antibodies. Thus, the term includes segments of proteolytically-cleaved or recombinantly-prepared portions of an antibody molecule that are capable of selectively reacting with a certain protein. Nonlimiting examples of such proteolytic and/or recombinant fragments include Fab, F(ab')<sub>2</sub>, Fab', Fv, and single chain antibodies (scFv) containing a V[L] and/or V[H] domain joined by a peptide linker. The scFv's may be covalently or non-covalently linked to form antibodies having two or more binding sites. The subject invention includes polyclonal, monoclonal, or other purified preparations of antibodies and recombinant antibodies.

**[0029]** As used herein, a "colorectal cancer associated marker" refers to a polypeptide or nucleic acid sequence which exhibits over- or underexpression of at least 10% in colorectal cancer cells, tissue, or serum obtained from an individual having colorectal cancer, relative to the level of expression in cells, tissue, or serum obtained from an individual that does not have colorectal cancer. Non-limiting examples of colorectal cancer associated markers useful in the present invention include the nucleic acid molecules of SEQ ID Nos 1, 3, 5-71, and/or the polypeptide molecules of SEQ ID Nos 2, 4, 72-138. In one embodiment, the polypeptide sequences of SEQ ID Nos 2, 4, 72-138 are encoded by the nucleic acid sequences of 1, 3, 5-71, respectively. A "colorectal cancer specific marker" useful in the invention may be a polypeptide or nucleic acid sequence which exhibits over- or underexpression in colorectal cancer as described above, but which may also be over or underexpressed in other, non-colorectal types of cancer. Alternatively, a "colorectal cancer associated marker", as used herein, may refer to a carbohydrate epitope present on a polypeptide or nucleic acid molecule and/or an antibody molecule which recognizes and is capable of binding to such an epitope, wherein the carbohydrate epitope is known to be associated with the presence of colorectal cancer in an individual. Such carbohydrate epitopes may be present on more than one unrelated protein or polypeptide. In one embodiment, such a carbohydrate epitope is CA 19-9, also known as sialyl-Lewis<sup>a</sup>, is a tumor marker defined by a monoclonal antibody as a carbohydrate epitope, related to the blood group antigens, composed of a branching, 5-sugar structure covalently bound to a variety of glycoproteins or glycolipids. The proteins primarily belong to the mucin family and the lipids are usually membrane associated. The CA 19-9 epitope is typically the terminal moiety of a complex, O-linked carbohydrate structure on either macromolecule. Other tumor markers also defined as various carbohydrate epitopes useful in the present invention as a "colorectal cancer associated marker" include CA 72-4, TF, sTn, Tn, CA 50, CA 549, CA 242, LASA, and the Du-PAN's 1-5.

**[0030]** The term "interact" as used herein is meant to include detectable interactions (e.g., biochemical interactions) between molecules, such as interaction between protein-protein, protein-nucleic acid, nucleic acid-nucleic acid, and protein-small molecule or nucleic acid-small molecule in nature.

**[0031]** As used herein, the term "nucleic acid" refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). The term should also be understood to include, as equivalents, analogs of either RNA or DNA made from nucleotide analogs, and, as applicable to the embodiment being described, single (sense or antisense) and double-stranded polynucleotides. ESTs, chromosomes, cDNAs, mRNAs, and rRNAs are representative examples of molecules that may be referred to as nucleic acids.

**[0032]** The terms "protein", "polypeptide", and "peptide" are used interchangeably herein when referring to a gene product. As used herein, "polypeptide" refers to any kind of polypeptide such as peptides, human proteins, fragments of human proteins, proteins or fragments of proteins from non-human sources, engineered versions proteins or fragments of proteins, enzymes, antigens, drugs, molecules involved in cell signaling, such as receptor molecules, antibodies, including polypeptides of the immunoglobulin superfamily, such as antibody polypeptides or T-cell receptor polypeptides.

**[0033]** As used herein, the term "level of expression" refers to the measurable expression level of a given nucleic acid. The level of expression of a nucleic acid is determined by methods well known in the art. The "level of expression" may measured by hybridization analysis using labeled target nucleic acids according to methods well known in the art (see, for example, Ausubel et al., Short Protocols in Molecular Biology, 3<sup>rd</sup> Ed. 1995, John Wiley and Sons, Inc.). The label on the target nucleic acid is a luminescent label, an enzymatic label, a radioactive label, a chemical label or a physical label. Preferably, the target nucleic acids are labeled with a fluorescent molecule. Preferred fluorescent labels include fluorescein, amino coumarin acetic acid, tetramethylrhodamine isothiocyanate (TRITC), Texas Red, Cy3 and Cy5. Alternatively, the "level of expression" can be measured by quantitative amplification protocols, such as TaqMan, known to those of skill in the art.

**[0034]** The term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of preferred vector is an episome, i. e., a nucleic acid capable of extra-chromosomal replication. Preferred vectors are those capable of autonomous replication and/or expression of nucleic acids to which they

are linked. Vectors capable of directing the expression of genes to which they are operatively linked are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of "plasmids" which refer generally to circular double stranded DNA loops which, in their vector form are not bound to the chromosome. In the present specification, "plasmid" and "vector" are used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors which serve equivalent functions and which become known in the art subsequently hereto.

#### Reg1 $\alpha$ and TIMP1 nucleic acid

**[0035]** As described above, the present invention relates to the detection of Reg1 $\alpha$  or TIMP1 polypeptide in a clinical sample from an individual, preferably a serum or plasma sample, thus permitting the detection of colorectal cancer. The present invention, however, equally relates to the identification of the nucleic acid sequence which encodes Reg1 $\alpha$  or TIMP1 as a marker for colorectal cancer.

**[0036]** Nucleic acid and amino acid sequences of Reg1 $\alpha$  are shown in SEQ ID Nos 1 or 3, and 2 or 4, respectively. Nucleic acid and amino acid sequences of TIMP1 are shown in SEQ ID NO: 33 and 100 respectively. While the invention relates to the direct detection of either of the sequences of Reg 1 $\alpha$  or TIMP1 in a method for detecting colorectal cancer, the invention further relates to the detection of sequences complementary thereto, or a sequence which specifically hybridizes to a sequence of SEQ ID Nos. 1, 3, or 33. The present invention also relates to the detection of colorectal cancer by detecting the presence, in a clinical sample, of a nucleic acid molecule which encodes the sequence of SEQ ID Nos. 2, 4, or 100, or a fragment thereof.

**[0037]** Another aspect of the invention provides the detection of colorectal cancer by the detection of a nucleic acid which hybridizes under low, medium, or high stringency conditions to a nucleic acid sequence represented by one or more of SEQ ID Nos. 1, 3, or 33, or a sequence complementary thereto. Appropriate stringency conditions which promote DNA hybridization, for example, 6.0 x sodium chloride/sodium citrate (SSC) at about 45 °C, followed by a wash of 2.0 x SSC at 50°C, are known to those skilled in the art or can be found in Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-12.3.6. For example, the salt concentration in the wash step can be selected from a low stringency of about 2.0 x SSC at 50°C to a high stringency of about 0.2 x SSC at 50°C. In addition, the temperature in the wash step can be increased from low stringency conditions at room temperature, about 22 °C, to high stringency conditions at about 65 °C. Both temperature and salt may be varied, or temperature or salt concentration may be held constant while the other variable is changed. In a preferred embodiment, a nucleic acid encoding Reg1 $\alpha$  or TIMP1 will bind to SEQ ID Nos. 1, 3 or 33, or a sequence complementary thereto, or a fragment thereof, under moderately stringent conditions, for example at about 2.0 x SSC and about 40°C. In a particularly preferred embodiment, a Reg1 $\alpha$  or TIMP1 nucleic acid sequence present in a patient clinical sample will bind of SEQ ID Nos. 1, 3, or 33, respectively, or a sequence complementary thereto, or fragment thereof, under high stringency conditions.

**[0038]** In one embodiment, the invention provides nucleic acids which hybridize under low stringency conditions of 6 x SSC at room temperature followed by a wash at 2 x SSC at room temperature.

**[0039]** In another embodiment, the invention provides nucleic acids which hybridize under high stringency conditions of 2 x SSC at about 65 °C followed by a wash at 0.2 x SSC at about 65 °C.

**[0040]** Detection of Reg1 $\alpha$  nucleic acids having a sequence that differs from the nucleotide sequences shown in SEQ ID Nos. 1 or 3, or a sequence complementary thereto, due to degeneracy in the genetic code, are also within the scope of the invention. Such nucleic acids encode functionally equivalent peptides (i.e., a peptide having equivalent or similar biological activity) but differ in sequence from the sequence shown in the sequence listing due to degeneracy in the genetic code. For example, a number of amino acids are designated by more than one triplet. Codons that specify the same amino acid, or synonyms (for example, CAU and CAC each encode histidine) may result in "silent" mutations which do not affect the amino acid sequence of a polypeptide. However, it is expected that DNA sequence polymorphisms that do lead to changes in the amino acid sequences of the subject polypeptides will exist among mammals. One skilled in the art will appreciate that these variations in one or more nucleotides (e.g., up to about 3-5% of the nucleotides) of the nucleic acids encoding polypeptides having an activity of a polypeptide may exist among individuals of a given species due to natural allelic variation.

**[0041]** The invention also includes within its scope a polynucleotide which hybridizes under stringent conditions (at least about 4 x SSC at 65 °C, or at least about 4 x SSC at 42 °C; see, for example, U.S. Patent No. 5,707,829, incorporated herein by reference) with at least 15 contiguous nucleotides of SEQ ID Nos. 1 or 3. By this is intended that when at least 15 contiguous nucleotides of SEQ ID Nos. 1 or 3 is used as a probe, the probe will preferentially hybridize with a gene or mRNA (of the biological material) comprising the complementary sequence, allowing the identification and retrieval of the nucleic acids (i.e., Reg1 $\alpha$ ) of the biological material that uniquely hybridize to the selected probe. Probes of more than 15 nucleotides can be used, but 15 nucleotides represents enough sequence for unique identification.

**[0042]** Constructs of polynucleotides having the sequence of SEQ ID Nos. 1 or 3, a portion thereof, or a sequence

complementary thereto, and useful, for example for generating a probe, can be produced synthetically, or obtained from natural sources (e.g., human cells) using methods well known to those of skill in the art (see, for example, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed. (Cold Spring Harbor Press, Cold Spring Harbor, NY 1989).

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#### *Calculation of Sequence Homology*

**[0043]** In one embodiment, the present invention relates to the detection of colorectal cancer in an individual by detecting the presence of Reg1 $\alpha$  or TIMP1 or a sequence homologous thereto, by using probes and/or primers which are complementary to portions of the Reg1 $\alpha$  or TIMP1 sequence, or are sufficiently homologous to portions of the Reg1 $\alpha$  or TIMP1 sequence to permit hybridization of the probes and/or primers to Reg1 $\alpha$  or TIMP1 under high stringency conditions. Sequences of the invention are at least 50% homologous to Reg1 $\alpha$  or TIMP1, and are preferably 60%, 70%, 80%, 90% homologous up to complete sequence identity with Reg1 $\alpha$  or TIMP1 (or optionally to a sequence encoding one or more additional colorectal cancer associated markers).

**[0044]** Sequence identity with respect to any of the sequences presented herein can be determined by a simple "eyeball" comparison (i.e. a strict comparison) of any one or more of the sequences with another sequence to see if that other sequence has, for example, at least 80% sequence identity to the sequence(s).

**[0045]** Relative sequence identity can also be determined by commercially available computer programs that can calculate % identity between two or more sequences using any suitable algorithm for determining identity, using for example default parameters. A typical example of such a computer program is CLUSTAL. Other computer program methods to determine identity and similarity between two sequences include but are not limited to the GCG program package (Devereux et al 1984 *Nucleic Acids Research* 12: 387) and FASTA (Atschul et al 1990 *J Molec Biol* 403-410).

**[0046]** % homology may be calculated over contiguous sequences, i.e. one sequence is aligned with the other sequence and each amino acid in one sequence is directly compared with the corresponding amino acid in the other sequence, one residue at a time. This is called an "ungapped" alignment. Typically, such ungapped alignments are performed only over a relatively short number of residues.

**[0047]** Although this is a very simple and consistent method, it fails to take into consideration that, for example, in an otherwise identical pair of sequences, one insertion or deletion will cause the following amino acid residues to be put out of alignment, thus potentially resulting in a large reduction in % homology when a global alignment is performed. Consequently, most sequence comparison methods are designed to produce optimal alignments that take into consideration possible insertions and deletions without penalising unduly the overall homology score. This is achieved by inserting "gaps" in the sequence alignment to try to maximise local homology.

**[0048]** However, these more complex methods assign "gap penalties" to each gap that occurs in the alignment so that, for the same number of identical amino acids, a sequence alignment with as few gaps as possible - reflecting higher relatedness between the two compared sequences - will achieve a higher score than one with many gaps. "Affine gap costs" are typically used that charge a relatively high cost for the existence of a gap and a smaller penalty for each subsequent residue in the gap. This is the most commonly used gap scoring system. High gap penalties will of course produce optimized alignments with fewer gaps. Most alignment programs allow the gap penalties to be modified. However, it is preferred to use the default values when using such software for sequence comparisons. For example, when using the GCG Wisconsin Bestfit package the default gap penalty for amino acid sequences is -12 for a gap and -4 for each extension.

**[0049]** Calculation of maximum % homology therefore firstly requires the production of an optimal alignment, taking into consideration gap penalties. A suitable computer program for carrying out such an alignment is the GCG Wisconsin Bestfit package (University of Wisconsin, U.S.A.; Devereux et al., 1984, *Nucleic Acids Research* 12:387). Examples of other software that can perform sequence comparisons include, but are not limited to, the BLAST package (Ausubel et al., 1995, *Short Protocols in Molecular Biology*, 3rd Edition, John Wiley & Sons), FASTA (Atschul et al., 1990, *J. Mol. Biol.*, 403-410) and the GENWORKS suite of comparison tools. Both BLAST and FASTA are available for offline and online searching (Ausubel et al., 1999 *supra*, pages 7-58 to 7-60).

**[0050]** Although the final % homology can be measured in terms of identity, the alignment process itself is typically not based on an all-or-nothing pair comparison. Instead, a scaled similarity score matrix is generally used that assigns scores to each pairwise comparison based on chemical similarity or evolutionary distance. An example of such a matrix commonly used is the BLOSUM62 matrix - the default matrix for the BLAST suite of programs. GCG Wisconsin programs generally use either the public default values or a custom symbol comparison table if supplied. It is preferred to use the public default values for the GCG package, or in the case of other software, the default matrix, such as BLOSUM62.

**[0051]** Advantageously, the BLAST algorithm is employed, with parameters set to default values. The BLAST algorithm is described in detail on the World Wide Web at [ncbi.nih.gov/BLAST/blast\\_help.html](http://ncbi.nih.gov/BLAST/blast_help.html), which is incorporated herein by reference. The search parameters are defined as follows, and can be advantageously set to the defined default

parameters.

**[0052]** Advantageously, "substantial identity" when assessed by BLAST equates to sequences which match with an EXPECT value of at least about 7, preferably at least about 9 and most preferably 10 or more. The default threshold for EXPECT in BLAST searching is usually 10.

5 **[0053]** BLAST (Basic Local Alignment Search Tool) is the heuristic search algorithm employed by the programs blastp, blastn, blastx, tblastn, and tblastx; these programs ascribe significance to their findings using the statistical methods of Karlin and Altschul (Karlin and Altschul 1990, *Proc. Natl. Acad. Sci. USA* 87:2264-68; Karlin and Altschul, 1993, *Proc. Natl. Acad. Sci. USA* 90:5873-7; see [http://www.ncbi.nlm.nih.gov/BLAST/blast\\_help.html](http://www.ncbi.nlm.nih.gov/BLAST/blast_help.html)) with a few enhancements. The BLAST programs are tailored for sequence similarity searching, for example to identify homologues to a query sequence. For a discussion of basic issues in similarity searching of sequence databases, see Altschul *et al*

10 (1994) *Nature Genetics* 6:119-129.  
**[0054]** The five BLAST programs available on the World Wide Web at [ncbi.nlm.nih.gov](http://ncbi.nlm.nih.gov) perform the following tasks: **blastp** - compares an amino acid query sequence against a protein sequence database; **blastn** - compares a nucleotide query sequence against a nucleotide sequence database; **blastx** - compares the six-frame conceptual translation products of a nucleotide query sequence (both strands) against a protein sequence database; **tblastn** - compares a protein query sequence against a nucleotide sequence database dynamically translated in all six reading frames (both strands); **tblastx** - compares the six-frame translations of a nucleotide query sequence against the six-frame translations of a nucleotide sequence database.

**[0055]** BLAST uses the following search parameters:

20 **[0056]** HISTOGRAM - Display a histogram of scores for each search; default is yes. (See parameter H in the BLAST Manual).

**[0057]** DESCRIPTIONS - Restricts the number of short descriptions of matching sequences reported to the number specified; default limit is 100 descriptions. (See parameter V in the manual page).

25 **[0058]** EXPECT - The statistical significance threshold for reporting matches against database sequences; the default value is 10, such that 10 matches are expected to be found merely by chance, according to the stochastic model of Karlin and Altschul (1990). If the statistical significance ascribed to a match is greater than the EXPECT threshold, the match will not be reported. Lower EXPECT thresholds are more stringent, leading to fewer chance matches being reported. Fractional values are acceptable. (See parameter E in the BLAST Manual).

30 **[0059]** CUTOFF - Cutoff score for reporting high-scoring segment pairs. The default value is calculated from the EXPECT value (see above). HSPs are reported for a database sequence only if the statistical significance ascribed to them is at least as high as would be ascribed to a lone HSP having a score equal to the CUTOFF value. Higher CUTOFF values are more stringent, leading to fewer chance matches being reported. (See parameter S in the BLAST Manual). Typically, significance thresholds can be more intuitively managed using EXPECT.

35 **[0060]** ALIGNMENTS - Restricts database sequences to the number specified for which high-scoring segment pairs (HSPs) are reported; the default limit is 50. If more database sequences than this happen to satisfy the statistical significance threshold for reporting (see EXPECT and CUTOFF below), only the matches ascribed the greatest statistical significance are reported. (See parameter B in the BLAST Manual).

40 **[0061]** MATRIX - Specify an alternate scoring matrix for BLASTP, BLASTX, TBLASTN and TBLASTX. The default matrix is BLOSUM62 (Henikoff & Henikoff, 1992). The valid alternative choices include: PAM40, PAM120, PAM250 and IDENTITY. No alternate scoring matrices are available for BLASTN; specifying the MATRIX directive in BLASTN requests returns an error response.

**[0062]** STRAND - Restrict a TBLASTN search to just the top or bottom strand of the database sequences; or restrict a BLASTN, BLASTX or TBLASTX search to just reading frames on the top or bottom strand of the query sequence.

45 **[0063]** FILTER - Mask off segments of the query sequence that have low compositional complexity, as determined by the SEG program of Wootton & Federhen (1993) *Computers and Chemistry* 17:149-163, or segments consisting of short-periodicity internal repeats, as determined by the XNU program of Claverie & States (1993) *Computers and Chemistry* 17:191-201, or, for BLASTN, by the DUST program of Tatusov and Lipman (see <http://www.ncbi.nlm.nih.gov>). Filtering can eliminate statistically significant but biologically uninteresting reports from the blast output (e.g., hits against common acidic-, basic- or proline-rich regions), leaving the more biologically interesting regions of the query sequence available for specific matching against database sequences.

50 **[0064]** Low complexity sequence found by a filter program is substituted using the letter "N" in nucleotide sequence (e.g., "NNNNNNNNNNNNNN") and the letter "X" in protein sequences (e.g., "XXXXXXXXXX").

**[0065]** Filtering is only applied to the query sequence (or its translation products), not to database sequences. Default filtering is DUST for BLASTN, SEG for other programs.

55 **[0066]** It is not unusual for nothing at all to be masked by SEG, XNU, or both, when applied to sequences in SWISS-PROT, so filtering should not be expected to always yield an effect. Furthermore, in some cases, sequences are masked in their entirety, indicating that the statistical significance of any matches reported against the unfiltered query sequence should be suspect.

**[0067]** NCBI-gi - Causes NCBI gi identifiers to be shown in the output, in addition to the accession and/or locus name.  
**[0068]** Most preferably, sequence comparisons are conducted using the simple BLAST search algorithm provided on the World Wide Web at [ncbi.nlm.nih.gov/BLAST](http://ncbi.nlm.nih.gov/BLAST). In some embodiments of the present invention, no gap penalties are used when determining sequence identity.

5

#### Probes and Primers

**[0069]** The nucleotide sequence of Reg1 $\alpha$  or TIMP1 is useful in the present invention for the generation of probes and primers designed for identifying the Reg1 $\alpha$  or TIMP1 nucleic acid sequence in a patient sample such as serum, colon cells or tissue. Nucleotide sequences useful as probes/primers may include all or a portion of SEQ ID Nos. 1, 3 or 33, or a sequence complementary thereto, or sequences which hybridize under stringent conditions to all or a portion of SEQ ID No. 1, 3 or 33. For instance, the present invention also provides a probe/primer comprising a substantially purified oligonucleotide, which oligonucleotide comprising a nucleotide sequence that hybridizes under stringent conditions to at least approximately 8, preferably about 12, preferably about 15, preferably about 25, more preferably about 40 consecutive nucleotides up to the full length of the sense or anti-sense sequence of SEQ ID Nos. 1, 3 or 33, or a sequence complementary thereto, or a naturally occurring mutant thereof. For instance, primers based on the nucleic acid represented in SEQ ID No. 1, 3 or 33, or a sequence complementary thereto, can be used in a reaction to amplify a template nucleic acid (e.g., Reg1 $\alpha$ ) contained within an mRNA sample derived from a patient clinical sample.

**[0070]** Not only are probes based on the nucleic acid sequence encoding Reg1 $\alpha$  or TIMP1 useful for detecting Reg1 $\alpha$  or TIMP1, but they can also provide a method for detecting mutations in wild-type Reg1 $\alpha$  or TIMP1 in a patient. Nucleic acid probes which are complementary to a wild-type Reg1 $\alpha$  or TIMP1 and can form mismatches with mutant genes are provided, allowing for detection by enzymatic or chemical cleavage or by shifts in electrophoretic mobility. Likewise, probes based on the subject sequences can be used to detect transcripts or genomic sequences encoding the same or homologous proteins, for use, for example, in prognostic or diagnostic assays. In preferred embodiments, the nucleic acid probe further comprises a label group attached thereto and able to be detected, e.g., the label group is selected from a radioisotope, a fluorescent compound, a chemiluminescent compound, a chromagenic compound, an enzyme, and enzyme co-factor.

**[0071]** Full-length cDNA molecules comprising the disclosed nucleic acids, useful for the generation of probes, primers, or for transcription to produce the Reg1 $\alpha$  or TIMP1 protein itself, or antibodies thereto may be obtained as follows. The nucleic acid sequence of Reg1 $\alpha$  or TIMP1 or a portion thereof comprising at least approximately 8, preferably about 12, preferably about 15, preferably about 25, more preferably about 40 nucleotides up to the full length of the sequence of SEQ ID Nos. 1, 3 or 33, or a sequence complementary thereto, may be used as a hybridization probe to detect hybridizing members of a cDNA library using probe design methods, cloning methods, and clone selection techniques as described in U.S. Patent No. 5,654,173, "Secreted Proteins and Polynucleotides Encoding Them," incorporated herein by reference. Libraries of cDNA may be made from selected tissues, such as normal or tumor tissue, or from tissues of a mammal treated with, for example, a pharmaceutical agent. Preferably, the tissue is the same as that used to generate the nucleic acids, as both the nucleic acid and the cDNA represent expressed genes. Alternatively, many cDNA libraries are available commercially. (Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed. (Cold Spring Harbor Press, Cold Spring Harbor, NY 1989). The choice of cell type for library construction may be made after the identity of the protein encoded by the nucleic acid-related gene is known. This will indicate which tissue and cell types are likely to express the related gene, thereby containing the mRNA for generating the cDNA.

**[0072]** Members of the library that are larger than the nucleic acid, and preferably that contain the whole sequence of the native message, may be obtained. To confirm that the entire cDNA has been obtained, RNA protection experiments may be performed as follows. Hybridization of a full-length cDNA to an mRNA may protect the RNA from RNase degradation. If the cDNA is not full length, then the portions of the mRNA that are not hybridized may be subject to RNase degradation. This may be assayed, as is known in the art, by changes in electrophoretic mobility on polyacrylamide gels, or by detection of released mononucleotides. Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed. (Cold Spring Harbor Press, Cold Spring Harbor, NY 1989). In order to obtain additional sequences 5' to the end of a partial cDNA, 5' RACE (PCR Protocols: A Guide to Methods and Applications (Academic Press, Inc. 1990)) may be performed.

**[0073]** Genomic DNA (e.g., Reg1 $\alpha$  genomic DNA) may be isolated using nucleic acids in a manner similar to the isolation of full-length cDNAs. Briefly, the nucleic acids, or portions thereof, may be used as probes to libraries of genomic DNA. Preferably, the library is obtained from the cell type that was used to generate the nucleic acids. Most preferably, the genomic DNA is obtained from the biological material described herein in the Example. Such libraries may be in vectors suitable for carrying large segments of a genome, such as P1 or YAC, as described in detail in Sambrook et al., pages 9.4-9.30. In addition, genomic sequences can be isolated from human BAC libraries, which are commercially available from Research Genetics, Inc., Huntsville, Alabama, USA, for example. In order to obtain addi-

tional 5' or 3' sequences, chromosome walking may be performed, as described in Sambrook et al., such that adjacent and overlapping fragments of genomic DNA are isolated. These may be mapped and pieced together, as is known in the art, using restriction digestion enzymes and DNA ligase.

**[0074]** Using the nucleic acids of the invention, corresponding full length genes can be isolated using both classical and PCR methods to construct and probe cDNA libraries. Using either method, Northern blots, preferably, may be performed on a number of cell types to determine which cell lines express the gene of interest at the highest rate.

**[0075]** Classical methods of constructing cDNA libraries in Sambrook et al., supra. With these methods, cDNA can be produced from mRNA and inserted into viral or expression vectors. Typically, libraries of mRNA comprising poly(A) tails can be produced with poly(T) primers. Similarly, cDNA libraries can be produced using the instant Reg1 $\alpha$  sequence or portions thereof as primers.

**[0076]** PCR methods may be used to amplify the members of a cDNA library that comprise the desired insert. In this case, the desired insert may contain sequence from the full length cDNA that corresponds to the sequence encoding Reg1 $\alpha$ . Such PCR methods include gene trapping and RACE methods.

**[0077]** Gene trapping may entail inserting a member of a cDNA library into a vector. The vector then may be denatured to produce single stranded molecules. Next, a substrate-bound probe, such a biotinylated oligo, may be used to trap cDNA inserts of interest. Biotinylated probes can be linked to an avidin-bound solid substrate. PCR methods can be used to amplify the trapped cDNA. To trap sequences corresponding to the full length genes, the labeled probe sequence may be based on the nucleic acid of SEQ ID Nos. 1 or 3, or a sequence complementary thereto. Random primers or primers specific to the library vector can be used to amplify the trapped cDNA. Such gene trapping techniques are described in Gruber et al., PCT WO 95/04745 and Gruber et al., U.S. Pat. No. 5,500,356. Kits are commercially available to perform gene trapping experiments from, for example, Life Technologies, Gaithersburg, Maryland, USA.

**[0078]** "Rapid amplification of cDNA ends," or RACE, is a PCR method of amplifying cDNAs from a number of different RNAs. The cDNAs may be ligated to an oligonucleotide linker and amplified by PCR using two primers. One primer may be based on sequence from the instant nucleic acids, for which full length sequence is desired, and a second primer may comprise a sequence that hybridizes to the oligonucleotide linker to amplify the cDNA. A description of this method is reported in PCT Pub. No. WO 97/19110.

**[0079]** In preferred embodiments of RACE, a common primer may be designed to anneal to an arbitrary adaptor sequence ligated to cDNA ends (Apte and Siebert, *Biotechniques* 15:890-893, 1993; Edwards et al., *Nuc. Acids Res.* 19:5227-5232, 1991). When a single gene-specific RACE primer is paired with the common primer, preferential amplification of sequences between the single gene specific primer and the common primer occurs. Commercial cDNA pools modified for use in RACE are available.

**[0080]** Once the full-length cDNA or gene is obtained, DNA encoding variants can be prepared by site-directed mutagenesis, described in detail in Sambrook 15.3-15.63. The choice of codon or nucleotide to be replaced can be based on the disclosure herein on optional changes in amino acids to achieve altered protein structure and/or function.

**[0081]** As an alternative method to obtaining DNA or RNA from a biological material, such as serum, nucleic acid comprising nucleotides having the sequence of one or more nucleic acids of the invention can be synthesized. Thus, the invention encompasses nucleic acid molecules ranging in length from about 8 nucleotides (corresponding to at least 12 contiguous nucleotides which hybridize under stringent conditions to or are at least 80% identical to the nucleic acid sequence of SEQ ID Nos. 1 or 3, or a sequence complementary thereto) up to a maximum length suitable for one or more biological manipulations, including replication and expression, of the nucleic acid molecule. The invention includes but is not limited to (a) nucleic acid having the size of the full Reg1 $\alpha$  gene, or a sequence complementary thereto; (b) the nucleic acid of (a) also comprising at least one additional gene, operably linked to permit expression of a fusion protein; (c) an expression vector comprising (a) or (b); (d) a plasmid comprising (a) or (b); and (e) a recombinant viral particle comprising (a) or (b).

**[0082]** The sequence of a nucleic acid of the present invention is not limited and can be any sequence of A, T, G, and/or C (for DNA) and A, U, G, and/or C (for RNA) or modified bases thereof, including inosine and pseudouridine. The choice of sequence will depend on the desired function and can be dictated by coding regions desired, the intron-like regions desired, and the regulatory regions desired.

#### *Probe preparation*

**[0083]** Prior to hybridization of a probe nucleic acid to a patient sample, the nucleic acid samples must be prepared to facilitate subsequent detection of hybridization. The nucleic acid samples obtained from an individual (including nucleic acid sequences encoding Reg1 $\alpha$ , and optionally, at least one other colorectal cancer associated marker) to be screened for colorectal cancer are capable of being bound by a nucleic acid probe of complementary sequence through one or more types of chemical bonds, usually through complementary base pairing, usually through hydrogen bond formation.

**[0084]** Probes useful in the invention for hybridizing to and thus identifying the presence of Reg1 $\alpha$  or TIMP1, and

optionally, at least one additional colorectal cancer associated marker may be designed to hybridize to a polynucleotide molecule derived from an mRNA transcript coding for Reg1 $\alpha$ , or optionally, at least one additional colorectal cancer associated marker. As used herein, a "polynucleotide derived from an mRNA transcript" refers to a polynucleotide for which synthesis of the mRNA transcript or a subsequence thereof has ultimately served as a template. Thus, a cDNA reverse transcribed from an mRNA, an RNA transcribed from that cDNA, a DNA amplified from the cDNA, an RNA transcribed from the amplified DNA, etc., are all derived from the mRNA transcript and detection of such derived products is indicative of the presence and/or abundance of the original transcript in a sample. Thus, suitable target nucleic acid samples include, but are not limited to, mRNA transcripts of a gene or genes (i.e., Reg1 $\alpha$  or a colorectal cancer associated marker), cDNA reverse transcribed from the mRNA, cRNA transcribed from the cDNA, DNA amplified from a gene or genes, RNA transcribed from amplified DNA, and the like. The polynucleotide probes used herein are preferably designed to hybridize to Reg1 $\alpha$ , or optionally to a sequence encoding at least one other colorectal cancer associated marker.

**[0085]** Nucleic acid probes may be generated using techniques which are well known to those of skill in the art (see, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual* (2nd ed.), Vols. 1-3, Cold Spring Harbor Laboratory, (1989), or *Current Protocols in Molecular Biology*, F. Ausubel et al., ed. Greene Publishing and Wiley-Interscience, New York (1987).

**[0086]** In order to measure the hybridization of a probe nucleic acid to a target sequence in a sample, the probe nucleic acid is preferably labeled with a detectable label. Any analytically detectable marker that is attached to or incorporated into a molecule may be used in the invention. An analytically detectable marker refers to any molecule, moiety or atom which is analytically detected and quantified.

**[0087]** Detectable labels suitable for use in the present invention include any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels in the present invention include biotin for staining with labeled streptavidin conjugate, magnetic beads (e.g., Dynabeads<sup>TM</sup>), fluorescent dyes (e.g., fluorescein, texas red, rhodamine, green fluorescent protein, and the like), radiolabels (e.g., <sup>3</sup>H, <sup>125</sup>I, <sup>35</sup>S, <sup>14</sup>C, or <sup>32</sup>P), enzymes (e.g., horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and colorimetric labels such as colloidal gold or colored glass or plastic (e.g., polystyrene, polypropylene, latex, etc.) beads. Patents teaching the use of such labels include U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241.

**[0088]** Means of detecting such labels are well known to those of skill in the art. Thus, for example, radiolabels may be detected using photographic film or scintillation counters, fluorescent markers may be detected using a photodetector to detect emitted light. Enzymatic labels are typically detected by providing the enzyme with a substrate and detecting the reaction product produced by the action of the enzyme on the substrate, and colorimetric labels are detected by simply visualizing the colored label.

**[0089]** The labels may be incorporated into a nucleic acid probe by any of a number of means well known to those of skill in the art. However, in a preferred embodiment, the label is simultaneously incorporated into the probe during an amplification step in the preparation of the probe polynucleotides. Thus, for example, polymerase chain reaction (PCR), or other amplification reaction, with labeled primers or labeled nucleotides will provide a labeled amplification product, and thus a labeled probe.

**[0090]** Alternatively, a label may be added directly to the probe. Means of attaching labels to polynucleotides are well known to those of skill in the art and include, for example nick translation or end-labeling (e.g. with a labeled RNA) and subsequent attachment (ligation) of a polynucleotide linker joining the sample polynucleotide to a label (e.g., a fluorophore).

**[0091]** In a preferred embodiment, the fluorescent modifications are by cyanine dyes e.g. Cy-3/Cy-5 dUTP, Cy-3/Cy-5 dCTP (Amersham Pharmacia) or alexa dyes (Khan, J., Simon, R., Bittner, M., Chen, Y., Leighton, S. B., Pohida, T., Smith, P. D., Jiang, Y., Gooden, G. C., Trent, J. M. & Meltzer, P. S. (1998) *Cancer Res.* 58, 50095013.).

**[0092]** In a preferred embodiment, a probe nucleic acid which is capable of hybridizing to Reg 1 $\alpha$  and a probe nucleic acid which is capable of hybridizing to a nucleic acid sequence encoding at least one additional colorectal cancer associated marker, are co-hybridized to a test sample (e.g., a serum sample). In this embodiment, the two probe samples used for comparison are labeled with different fluorescent dyes which produce distinguishable detection signals, for example, probes hybridizable with Reg 1 $\alpha$  are labeled with Cy5 and probes hybridizable with another colorectal cancer associated marker are labeled with Cy3. The differently labeled target samples are hybridized to the same microarray simultaneously.

**[0093]** In a preferred embodiment, a control probe may be co-hybridized to a sample along with a probe for Reg1 $\alpha$  and/or a probe for an additional colorectal cancer associated marker, wherein the control probe is capable of hybridizing to a nucleic acid sequence known to be found in the clinical sample, for example, where the clinical sample is a serum sample, a control sequence may be a sequence encoding serum albumin, or fibrinogen.

Vectors and Host Cells

**[0094]** The present invention further provides vectors and plasmids useful for directing the expression of Reg1 $\alpha$  or TIMP1 or other colorectal cancer associated markers, and further provides host cells which express the vectors and plasmids provided herein. Nucleic acid sequences useful for the expression from a vector or plasmid as described below include, but are not limited to any nucleic acid or gene sequence identified as being differentially regulated by the methods described above, and further include therapeutic nucleic acid molecules, such as antisense molecules. The host cell may be any prokaryotic or eukaryotic cell. Ligating the polynucleotide sequence into a gene construct, such as an expression vector, and transforming or transfecting into hosts, either eukaryotic (yeast, avian, insect or mammalian) or prokaryotic (bacterial cells), are standard procedures well known in the art.

Vectors

**[0095]** There is a wide array of vectors known and available in the art that are useful for the expression of differentially expressed nucleic acid molecules according to the invention. The selection of a particular vector clearly depends upon the intended use the polypeptide encoded by the differentially expressed nucleic acid. For example, the selected vector must be capable of driving expression of the polypeptide in the desired cell type, whether that cell type be prokaryotic or eukaryotic. Many vectors comprise sequences allowing both prokaryotic vector replication and eukaryotic expression of operably linked gene sequences.

**[0096]** Vectors useful according to the invention may be autonomously replicating, that is, the vector, for example, a plasmid, exists extrachromosomally and its replication is not necessarily directly linked to the replication of the host cell's genome. Alternatively, the replication of the vector may be linked to the replication of the host's chromosomal DNA, for example, the vector may be integrated into the chromosome of the host cell as achieved by retroviral vectors.

**[0097]** Vectors useful according to the invention preferably comprise sequences operably linked to the sequence of interest (e.g., Reg1 $\alpha$ ) that permit the transcription and translation of the sequence. Sequences that permit the transcription of the linked sequence of interest include a promoter and optionally also include an enhancer element or elements permitting the strong expression of the linked sequences. The term "transcriptional regulatory sequences" refers to the combination of a promoter and any additional sequences conferring desired expression characteristics (e.g., high level expression, inducible expression, tissue- or cell-type-specific expression) on an operably linked nucleic acid sequence.

**[0098]** The selected promoter may be any DNA sequence that exhibits transcriptional activity in the selected host cell, and may be derived from a gene normally expressed in the host cell or from a gene normally expressed in other cells or organisms. Examples of promoters include, but are not limited to the following: A) prokaryotic promoters - *E. coli* lac, tac, or trp promoters, lambda phage P<sub>R</sub> or P<sub>L</sub> promoters, bacteriophage T7, T3, Sp6 promoters, *B. subtilis* alkaline protease promoter, and the *B. stearothermophilus* maltogenic amylase promoter, etc.; B) eukaryotic promoters - yeast promoters, such as GAL1, GAL4 and other glycolytic gene promoters (see for example, Hitzeman et al., 1980, J. Biol. Chem. 255: 12073-12080; Alber & Kawasaki, 1982, J. Mol. Appl. Gen. 1: 419-434), LEU2 promoter (Martinez-Garcia et al., 1989, Mol Gen Genet. 217: 464-470), alcohol dehydrogenase gene promoters (Young et al., 1982, in Genetic Engineering of Microorganisms for Chemicals, Hollaender et al., eds., Plenum Press, NY), or the TP11 promoter (U.S. Pat. No. 4,599,311); insect promoters, such as the polyhedrin promoter (U.S. Pat. No. 4,745,051; Vasuvedan et al., 1992, FEBS Lett. 311: 7-11), the P10 promoter (Vlak et al., 1988, J. Gen. Virol. 69: 765-776), the *Autographa californica* polyhedrosis virus basic protein promoter (EP 397485), the baculovirus immediate-early gene promoter gene 1 promoter (U.S. Pat. Nos. 5,155,037 and 5,162,222), the baculovirus 39K delayed-early gene promoter (also U.S. Pat. Nos. 5,155,037 and 5,162,222) and the OpMNPV immediate early promoter 2; mammalian promoters - the SV40 promoter (Subramani et al., 1981, Mol. Cell. Biol. 1: 854-864), metallothionein promoter (MT-1; Palmiter et al., 1983, Science 222: 809-814), adenovirus 2 major late promoter (Yu et al., 1984, Nucl. Acids Res. 12: 9309-21), cytomegalovirus (CMV) or other viral promoter (Tong et al., 1998, Anticancer Res. 18: 719-725), or even the endogenous promoter of a gene of interest in a particular cell type.

**[0099]** A selected promoter may also be linked to sequences rendering it inducible or tissue-specific. For example, the addition of a tissue-specific enhancer element upstream of a selected promoter may render the promoter more active in a given tissue or cell type. Alternatively, or in addition, inducible expression may be achieved by linking the promoter to any of a number of sequence elements permitting induction by, for example, thermal changes (temperature sensitive), chemical treatment (for example, metal ion- or IPTG-inducible), or the addition of an antibiotic inducing agent (for example, tetracycline).

**[0100]** Regulatable expression is achieved using, for example, expression systems that are drug inducible (e.g., tetracycline, rapamycin or hormone-inducible). Drug-regulatable promoters that are particularly well suited for use in mammalian cells include the tetracycline regulatable promoters, and glucocorticoid steroid-, sex hormone steroid-, ecdysone-, lipopolysaccharide (LPS)- and isopropylthiogalactoside (IPTG)-regulatable promoters. A regulatable ex-



pression system for use in mammalian cells should ideally, but not necessarily, involve a transcriptional regulator that binds (or fails to bind) nonmammalian DNA motifs in response to a regulatory agent, and a regulatory sequence that is responsive only to this transcriptional regulator.

**[0101]** Tissue-specific promoters may also be used to advantage in differentially expressed sequence-encoding constructs of the invention. A wide variety of tissue-specific promoters is known. As used herein, the term "tissue-specific" means that a given promoter is transcriptionally active (i.e., directs the expression of linked sequences sufficient to permit detection of the polypeptide product of the promoter) in less than all cells or tissues of an organism. A tissue specific promoter is preferably active in only one cell type, but may, for example, be active in a particular class or lineage of cell types (e.g., hematopoietic cells). A tissue specific promoter useful according to the invention comprises those sequences necessary and sufficient for the expression of an operably linked nucleic acid sequence in a manner or pattern that is essentially the same as the manner or pattern of expression of the gene linked to that promoter in nature. The following is a non-exclusive list of tissue specific promoters and literature references containing the necessary sequences to achieve expression characteristic of those promoters in their respective tissues; the entire content of each of these literature references is incorporated herein by reference. Examples of tissue specific promoters useful in the present invention are as follows:

**[0102]** Bowman et al., 1995 Proc. Natl. Acad. Sci. USA 92, 12115-12119 describe a brain-specific transferrin promoter; the synapsin I promoter is neuron specific (Schoch et al., 1996 J. Biol. Chem. 271, 3317-3323); the nestin promoter is post-mitotic neuron specific (Uetsuki et al., 1996 J. Biol. Chem. 271, 918-924); the neurofilament light promoter is neuron specific (Charron et al., 1995 J. Biol. Chem. 270, 30604-30610); the acetylcholine receptor promoter is neuron specific (Wood et al., 1995 J. Biol. Chem. 270, 30933-30940); and the potassium channel promoter is high-frequency firing neuron specific (Gan et al., 1996 J. Biol. Chem. 271, 5859-5865). Any tissue specific transcriptional regulatory sequence known in the art may be used to advantage with a vector encoding a differentially expressed nucleic acid sequence obtained from an animal subjected to pain.

**[0103]** In addition to promoter/enhancer elements, vectors useful according to the invention may further comprise a suitable terminator. Such terminators include, for example, the human growth hormone terminator (Palmiter et al., 1983, supra), or, for yeast or fungal hosts, the TPI1 (Alber & Kawasaki, 1982, supra) or ADH3 terminator (McKnight et al., 1985, EMBO J. 4: 2093-2099).

**[0104]** Vectors useful according to the invention may also comprise polyadenylation sequences (e.g., the SV40 or Ad5E1b poly(A) sequence), and translational enhancer sequences (e.g., those from Adenovirus VA RNAs). Further, a vector useful according to the invention may encode a signal sequence directing the recombinant polypeptide to a particular cellular compartment or, alternatively, may encode a signal directing secretion of the recombinant polypeptide.

#### a. Plasmid vectors.

**[0105]** Any plasmid vector that allows expression of a coding sequence of interest (e.g., the coding sequence of Reg1 $\alpha$ ) in a selected host cell type is acceptable for use according to the invention. A plasmid vector useful in the invention may have any or all of the above-noted characteristics of vectors useful according to the invention. Plasmid vectors useful according to the invention include, but are not limited to the following examples: Bacterial - pQE70, pQE60, pQE-9 (Qiagen) pBs, phagescript, psiX174, pBluescript SK, pBsKS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene); pTrc99A, pKK223-3, pKK233-3, pDR540, and pRIT5 (Pharmacia); Eukaryotic - pWLneo, pSV2cat, pOG44, pXT1, pSG (Stratagene) pSVK3, pBPV, pMSG, and pSVL (Pharmacia). However, any other plasmid or vector may be used as long as it is replicable and viable in the host.

#### b. Bacteriophage vectors.

**[0106]** There are a number of well known bacteriophage-derived vectors useful according to the invention. Foremost among these are the lambda-based vectors, such as Lambda Zap II or Lambda-Zap Express vectors (Stratagene) that allow inducible expression of the polypeptide encoded by the insert. Others include filamentous bacteriophage such as the M13-based family of vectors.

#### c. Viral vectors.

**[0107]** A number of different viral vectors are useful according to the invention, and any viral vector that permits the introduction and expression of one or more of the polynucleotides of the invention in cells is acceptable for use in the methods of the invention. Viral vectors that can be used to deliver foreign nucleic acid into cells include but are not limited to retroviral vectors, adenoviral vectors, adeno-associated viral vectors, herpesviral vectors, and Semliki forest viral (alphaviral) vectors. Defective retroviruses are well characterized for use in gene transfer (for a review see Miller,

A.D. (1990) *Blood* 76:271). Protocols for producing recombinant retroviruses and for infecting cells *in vitro* or *in vivo* with such viruses can be found in Current Protocols in Molecular Biology, Ausubel, F.M. et al. (eds.) Greene Publishing Associates, (1989), Sections 9.10-9.14, and other standard laboratory manuals.

[0108] In addition to retroviral vectors, Adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms of its ability to replicate in a normal lytic viral life cycle (see for example Berkner et al., 1988, *BioTechniques* 6:616; Rosenfeld et al., 1991, *Science* 252:431-434; and Rosenfeld et al., 1992, *Cell* 68:143-155). Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 dl324 or other strains of adenovirus (e.g., Ad2, Ad3, Ad7 etc.) are well known to those skilled in the art. Adeno-associated virus (AAV) is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. (For a review see Muzyczka et al., 1992, *Curr. Topics in Micro. and Immunol.* 158:97-129). An AAV vector such as that described in Traschin et al. (1985, *Mol. Cell. Biol.* 5:3251-3260) can be used to introduce nucleic acid into cells. A variety of nucleic acids have been introduced into different cell types using AAV vectors. (see, for example, Hermonat et al., 1984, *Proc. Natl. Acad. Sci. USA* 81: 6466-6470; and Traschin et al., 1985, *Mol. Cell. Biol.* 4: 2072-2081).

#### *Host cells*

[0109] Any cell into which a recombinant vector carrying a gene of interest (e.g., a sequence encoding Reg1 $\alpha$ ) may be introduced and wherein the vector is permitted to drive the expression of the peptide encoded by the differentially expressed sequence is useful according to the invention. Any cell in which a differentially expressed molecule of the invention may be expressed and preferably detected is a suitable host, wherein the host cell is preferably a mammalian cell and more preferably a human cell. Vectors suitable for the introduction of nucleic acid sequences to host cells from a variety of different organisms, both prokaryotic and eukaryotic, are described herein above or known to those skilled in the art.

[0110] Host cells may be prokaryotic, such as any of a number of bacterial strains, or may be eukaryotic, such as yeast or other fungal cells, insect or amphibian cells, or mammalian cells including, for example, rodent, simian or human cells. Cells may be primary cultured cells, for example, primary human fibroblasts or keratinocytes, or may be an established cell line, such as NIH3T3, 293T or CHO cells. Further, mammalian cells useful in the present invention may be phenotypically normal or oncogenically transformed. It is assumed that one skilled in the art can readily establish and maintain a chosen host cell type in culture.

#### *Introduction of vectors to host cells.*

[0111] Vectors useful in the present invention may be introduced to selected host cells by any of a number of suitable methods known to those skilled in the art. For example, vector constructs may be introduced to appropriate bacterial cells by infection, in the case of *E. coli* bacteriophage vector particles such as lambda or M 13, or by any of a number of transformation methods for plasmid vectors or for bacteriophage DNA. For example, standard calcium-chloride-mediated bacterial transformation is still commonly used to introduce naked DNA to bacteria (Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY), but electroporation may also be used (Ausubel et al., 1988, Current Protocols in Molecular Biology, (John Wiley & Sons, Inc., NY, NY)).

[0112] For the introduction of vector constructs to yeast or other fungal cells, chemical transformation methods are generally used (e.g. as described by Rose et al., 1990, Methods in Yeast Genetics, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY). For transformation of *S. cerevisiae*, for example, the cells are treated with lithium acetate to achieve transformation efficiencies of approximately 10<sup>4</sup> colony-forming units (transformed cells)/ $\mu$ g of DNA. Transformed cells are then isolated on selective media appropriate to the selectable marker used. Alternatively, or in addition, plates or filters lifted from plates may be scanned for GFP fluorescence to identify transformed clones.

[0113] For the introduction of vectors comprising a sequence of interest to mammalian cells, the method used will depend upon the form of the vector. Plasmid vectors may be introduced by any of a number of transfection methods, including, for example, lipid-mediated transfection ("lipofection"), DEAE-dextran-mediated transfection, electroporation or calcium phosphate precipitation. These methods are detailed, for example, in Current Protocols in Molecular Biology (Ausubel et al., 1988, John Wiley & Sons, Inc., NY, NY).

[0114] Lipofection reagents and methods suitable for transient transfection of a wide variety of transformed and non-transformed or primary cells are widely available, making lipofection an attractive method of introducing constructs to eukaryotic, and particularly mammalian cells in culture. For example, LipofectAMINE™ (Life Technologies) or LipoTaxi™ (Stratagene) kits are available. Other companies offering reagents and methods for lipofection include Bio-Rad Laboratories, CLONTECH, Glen Research, In Vitrogen, JBL Scientific, MBI Fermentas, PanVera, Promega, Quantum Biotechnologies, Sigma-Aldrich, and Wako Chemicals USA.

[0115] Following transfection with a vector of the invention, eukaryotic (e.g., human) cells successfully incorporating the construct (intra- or extrachromosomally) may be selected, as noted above, by either treatment of the transfected population with a selection agent, such as an antibiotic whose resistance gene is encoded by the vector, or by direct screening using, for example, FACS of the cell population or fluorescence scanning of adherent cultures. Frequently, both types of screening may be used, wherein a negative selection is used to enrich for cells taking up the construct and FACS or fluorescence scanning is used to further enrich for cells expressing differentially expressed polynucleotides or to identify specific clones of cells, respectively. For example, a negative selection with the neomycin analog G418 (Life Technologies, Inc.) may be used to identify cells that have received the vector, and fluorescence scanning may be used to identify those cells or clones of cells that express the vector construct to the greatest extent.

#### Reg1 $\alpha$ and TIMP1 Polypeptides

[0116] The present invention provides a method for the detection of colorectal cancer in an individual by detecting the presence of Reg1 $\alpha$  or TIMP1 in a clinical sample from an individual. In addition the invention encompasses the detection of cancer by identifying Reg1 $\alpha$  or TIMP1 gene product in colon tissue or cells. Alternatively, the invention relates to a method for the detection of colorectal cancer in an individual wherein colorectal cancer is identified by detecting the presence of Reg1 $\alpha$  or TIMP1 and at least one additional colorectal cancer associated marker in the clinical sample from an individual. Polypeptides of the present invention, the detection of which is indicative of colorectal cancer include those having the sequence shown in one or more of SEQ ID Nos. 2, 4, or 100, or alternatively, which are encoded by one or more of SEQ ID Nos. 1, 3 or 33.

[0117] Preferred polypeptides which can be detected and are thus indicative of colorectal cancer in an individual are those that are encoded by nucleic acid sequences at least about 70%, 75%, 80%, 90%, 95%, 97%, or 98% identical to a mRNA sequence complementary to the nucleic acid sequence of SEQ ID Nos. 1, 3 or 33. Particularly preferred polypeptides are those of SEQ ID Nos. 2, 4, or 99, or fragments thereof, or polypeptide sequences which are at least about 70%, 75%, 80%, 90%, 95%, 98% or 99% identical in sequence to the amino acid sequence of one or more of SEQ ID Nos. 2, 4, or 100.

[0118] In addition to a method for detecting colorectal cancer by identifying the presence of the Reg1 $\alpha$  or TIMP1 polypeptide in a clinical sample from an individual, the invention further comprises a method of detecting cancer by identifying the presence of Reg1 $\alpha$  or TIMP1 in addition to at least one other colorectal cancer associated marker in the same sample (e.g., in the same serum, tissue, or cell sample).

#### Antibodies

[0119] The invention provides a method for colorectal cancer detection comprising the step of detecting the presence of Reg1 $\alpha$  or TIMP1 (and optionally, at least one additional colorectal cancer associated marker) in a clinical sample from an individual. In one embodiment, the presence of Reg1 $\alpha$  or TIMP1, or other marker, in such a sample is detected using a polypeptide ligand which is preferably detectably labeled, and is capable of binding to Reg1 $\alpha$  or TIMP1, and if present, the other marker, in the sample. In a preferred embodiment, the polypeptide ligand is an antibody. Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized, or chimeric antibodies, single chain antibodies, Fab fragments, Fv fragments F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic antibodies, or other epitope binding polypeptide. Preferably, an antibody, useful in the present invention for the detection of Reg1 $\alpha$  or TIMP1 (and optionally at least one additional colorectal cancer associated marker), is a human antibody or fragment thereof, including scFv, Fab, Fab', F(ab'), Fd, single chain antibody, or Fv. Antibodies, useful in the invention may include a complete heavy or light chain constant region, or a portion thereof, or an absence thereof. An antibody, useful in the invention, may be obtained from an art recognized host, such as rabbit, mouse, rat, donkey, sheep, goat, guinea pig, camel, horse, or chicken. In one embodiment, an antibody, useful in the invention can be a humanized antibody, in which amino acids have been replaced in the non-antigen binding regions in order to more closely resemble a human antibody, while still retaining the original binding ability. Methods for making humanized antibodies are described in Teng et al., 1983, *Proc. Natl. Acad. Sci. USA* 80: 7308-7312; Kozbor et al., 1983, *Immunology Today* 4: 7279; Olsson et al., 1982, *Meth. Enzymol.* 92: 3-16; WO 92/06193; EP 0239400.

[0120] Antibodies of the present invention may be monospecific, dispecific, trispecific, or of greater multispecificity. As such, Reg1 $\alpha$  or TIMP1 and optionally an additional colorectal cancer associated marker useful for the detection of colorectal cancer may be detected with separate antibodies, or may be detected with the same antibody. Alternatively, a multispecific antibody may exhibit different specificities for different epitopes on the same protein (e.g., different epitopes on Reg1 $\alpha$ ). While specificity of an antibody useful in the present invention to either Reg1 $\alpha$  or one or more additional colorectal cancer associated markers is preferred, antibodies that bind polypeptides with at least 95%, 90%, 85%, 75%, 65%, 55%, and at least 50% identity to a polypeptide useful in the present invention for the detection of

colorectal cancer (i.e., Reg1 $\alpha$ , and/or an additional colorectal cancer associated marker) are also included in the present invention. Also encompassed in the present invention are antibodies which bind to polypeptide molecules which are encoded by one or more nucleic acid sequences which are complementary to, or hybridize to the sequences of SEQ ID Nos. 1, 3 or 33, or one or more sequences which are complementary to, or hybridize to a nucleic acid sequence which encodes an additional colorectal cancer associated marker as described herein.

**[0121]** Antibodies of the present invention which are useful for the detection of colorectal cancer may further act as agonists or antagonists of the activity of the polypeptide molecules to which they bind, and may thus be useful as therapeutic molecules for the treatment or prevention of colorectal cancer.

**[0122]** An important, but not limiting, role of an antibody of the present invention is to provide for the purification, or detection of Reg 1 $\alpha$  or TIMP1 or other colorectal cancer associated markers in a patient sample, including both in vitro and in vivo detection methods. Antibodies useful for the detection of colorectal cancer as described herein do not have to be used alone, and can be fused to other polypeptides, including a heterologous polypeptide at the N- or C-terminus of the antibody polypeptide sequence. For example, an antibody useful in the present invention may be fused with a detectable label to facilitate detection of the antibody when bound to a target polypeptide. Methods for detectably labeling an antibody polypeptide are known to those of skill in the art.

**[0123]** For the production of antibodies useful in the present invention, various hosts including goats, rabbits, rats, mice, etc., may be immunized by injection with the protein products (or any portion, fragment, or oligonucleotide thereof which retains immunogenic properties) of the candidate genes of the invention. Depending on the host species, various adjuvants may be used to increase the immunological response. Such adjuvants include but are not limited to Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, poly-anions, peptides, oil emulsions, keyhole limpet hemocyanin, and dinitrophenol. BCG (bacilli Calmette-Guerin) and *Corynebacterium parvum* are potentially useful human adjuvants.

**[0124]** Polyclonal antisera or monoclonal antibodies can be made using methods known in the art. A mammal such as a mouse, hamster, or rabbit, can be immunized with an immunogenic form of a Reg1 $\alpha$  or TIMP1 polypeptide, fragment, modified form thereof, or variant form thereof. Alternatively, an animal may be immunized with an immunogenic form of one or more additional colorectal cancer associated marker polypeptides. Techniques for conferring immunogenicity on such molecules include conjugation to carriers or other techniques well known in the art. For example, the immunogenic molecule can be administered in the presence of adjuvant as described above. Immunization can be monitored by detection of antibody titers in plasma or serum. Standard immunoassay procedures can be used with the immunogen as antigen to assess the levels and the specificity of antibodies. Following immunization, antisera can be obtained and, if desired, polyclonal antibodies isolated from the sera.

**[0125]** To produce monoclonal antibodies, antibody producing cells (lymphocytes) can be harvested from an immunized animal and fused with myeloma cells by standard somatic cell fusion procedures thus immortalizing these cells and yielding hybridoma cells. Such techniques are well known in the art (see, e.g., Kohler and Milstein, 1975, *Nature* 256: 495-497; Kozbor et al., 1983, *Immunol. Today* 4: 72; Cole et al., 1985, In *Monoclonal Antibodies in Cancer Therapy*, Allen R. Bliss, Inc., pages 77-96). Additionally, techniques described for the production of single-chain antibodies (U. S. Patent No. 4,946,778) can be adapted to produce antibodies according to the invention.

**[0126]** Antibody fragments which can specifically bind to a polypeptide of the invention such as Reg1 $\alpha$  or TIMP1 or other colorectal cancer associated marker polypeptides, fragments thereof, modified forms thereof, and variants thereof, also may be generated by known techniques. For example, such fragments include, but are not limited to, F(ab')<sub>2</sub> fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the F(ab')<sub>2</sub> fragments. VH regions and FV regions can be expressed in bacteria using phage expression libraries (e.g., Ward et al., 1989, *Nature* 341: 544-546; Huse et al., 1989, *Science* 246: 1275-1281; McCafferty et al., 1990, *Nature* 348: 552-554).

**[0127]** Chimeric antibodies, i.e., antibody molecules that combine a non-human animal variable region and a human constant region also are within the scope of the invention. Chimeric antibody molecules include, for example, the antigen binding domain from an antibody of a mouse, rat, or other species, with human constant regions. Standard methods may be used to make chimeric antibodies containing the immunoglobulin variable region which recognizes the gene product of Reg1 $\alpha$  antigens of the invention (see, e.g., Morrison et al., 1985, *Proc. Natl. Acad. Sci. USA* 81: 6851; Takeda et al., 1985, *Nature* 314: 452; U.S. Patent No. 4,816,567; U.S. Patent No. 4,816,397).

#### Other Colorectal cancer Specific Analysis

**[0128]** In addition to the detection of colorectal cancer by identifying expression of Reg1 $\alpha$  or TIMP1, or detecting Reg1 $\alpha$  or TIMP1 polypeptides, the present invention further comprises a method for detecting colorectal cancer wherein a nucleic acid molecule encoding Reg1 $\alpha$  or TIMP1, or Reg 1 $\alpha$  or TIMP 1 polypeptide is identified in combination with at least one other nucleic acid sequence encoding a known colorectal cancer associated marker in a clinical sample from an individual. Alternatively, the presence of Reg1 $\alpha$  or TIMP1 is detected in combination with at least one additional

colorectal cancer marker amino acid sequence. Similar to the methods described above for Reg1 $\alpha$ , a nucleic acid molecule which encodes at least one other colorectal cancer associated marker may be used to generate a nucleic acid probe for detection of the colorectal cancer associated marker sequence in a patient sample, or may be used to generate amplification primers to amplify the colorectal cancer associated marker sequence from a patient sample comprising the sequence, thus identifying the presence of the colorectal cancer associated marker in the sample, and thus indicating the detection of colorectal cancer. A colorectal cancer associated marker polypeptide sequence may be used, as described above for Reg1 $\alpha$  to generate antibodies useful for detection of the colorectal cancer associated marker in a clinical sample. Methods for detecting a colorectal cancer associated marker nucleic acid or amino acid sequence are described below, and may be adapted from the methods for the detection of Reg1 $\alpha$  nucleic acid or amino acid in a clinical sample.

A "colorectal cancer associated marker" useful in the present invention, refers to a polypeptide or nucleic acid sequence which exhibits over- or underexpression of at least 10% in colorectal cancer cells, tissue, or serum obtained from an individual having colorectal cancer, relative to the level of expression in cells, tissue, or serum obtained from an individual that does not have colorectal cancer. Non-limiting examples of colorectal cancer associated markers useful in the present invention include the nucleic acid molecules of SEQ ID Nos 1, 3, 5-71, and/or the polypeptide molecules of SEQ ID Nos 2, 4, 72-138. In one embodiment, the polypeptide sequences of SEQ ID Nos 2, 4, 72-138 are encoded by the nucleic acid sequences of 1, 3, 5-71, respectively. It will be appreciated by one of skill in the art that, where the method of the invention relates to detection of Reg1 $\alpha$  and at least one other colorectal cancer associated marker, TIMP1 may be included as a potential "other colorectal cancer associated marker". Likewise, where the detection method is based on the detection of TIMP1 and at least one other colorectal cancer associated marker, Reg1 $\alpha$  may be included as a potential "other colorectal cancer associated marker". Alternatively, a colorectal cancer associated marker, as used in the present invention, may refer to a carbohydrate epitope present on a polypeptide or nucleic acid molecule and/or an antibody molecule which recognizes and is capable of binding to such an epitope, wherein the carbohydrate epitope is known to be associated with the presence of colorectal cancer in an individual. Such carbohydrate epitopes may be present on more than one unrelated protein or polypeptide. In one embodiment, such a carbohydrate epitope is CA 19-9, also known as sialyl-Lewis<sup>a</sup>, is a tumor marker defined by a monoclonal antibody as a carbohydrate epitope, related to the blood group antigens, composed of a branching, 5-sugar structure covalently bound to a variety of glycoproteins or glycolipids. The proteins primarily belong to the mucin family and the lipids are usually membrane associated. The CA 19-9 epitope is typically the terminal moiety of a complex, O-linked carbohydrate structure on either macromolecule. Other tumor markers also defined as various carbohydrate epitopes useful in the present invention as a "colorectal cancer associated marker" include CA72-4 which is indicative of the presence of the Tag 72 antigen, which is a triply sialylated Tn antigen on varying protein backbones; Thomsen Freidenreich antigen (TF), which is a sialylated n-acetyl galactosamine moiety O-linked to various peptides; Tn and sialylated Tn (sTn) which is the backbone of the TF antigen without the terminal n-acetyl galactosamine moiety, O-linked to various peptides; CA 50 which is an epitope corresponding to sialylated Lewis A blood group antigen; CA 549 which is a CHO moiety on muc-1; CA 242 which is a sialylated CHO; LASA which is a lipid associated sialic acid, that is, a lipid without a protein associated to it; Du-PAN's 1-5, which are pancreatic associated mucin-like CHO antigens. These useful colon cancer specific antigens and others are known in the art and are described, for example, in "Serological Cancer Markers" Sell, S., Ed. 1992. Humana Press Inc., Totowa, NJ.

[0129] Table 1 below shows a list of "colorectal cancer associated markers" useful in the invention (although colorectal cancer associated markers useful in the invention are not limited to those shown in Table 1), and there correspondence with the sequences set forth in the "Sequence listing".

Table 1

SEQ ID NO	Gene Symbol	Length	Type	SEQ ID NO	Gene Symbol	Length	Type
5	CEACAM5	2974	DNA	72	CEACAM5	702	Protein
6	AFP	2032	DNA	73	AFP	609	Protein
7	IL8	1639	DNA	74	IL8	99	Protein
8	SPP1	1524	DNA	75	SPP1	300	Protein
9	KIAA1077	5500	DNA	76	KIAA1077	871	Protein
10	MMP12	1778	DNA	77	MMP12	470	Protein

11	UBD	777	DNA	78	UBD	165	Protein
12	COL1A1	5921	DNA	79	COL1A1	1464	Protein
13	LUM	1804	DNA	80	LUM	338	Protein
14	ENC1	4827	DNA	81	ENC1	589	Protein
15	PIGPC1	1098	DNA	82	PIGPC1	193	Protein
16	GTF3A	1381	DNA	83	GTF3A	423	Protein
17	CTSB	1978	DNA	84	CTSB	339	Protein
18	MCJ	1074	DNA	85	MCJ	150	Protein
19	SLC12A2	4098	DNA	86	SLC12A2	1212	Protein
20	C20orf42	3120	DNA	87	C20orf42	230	Protein
21	SDBCAG84	1337	DNA	88	SDBCAG84	383	Protein
22	NAP1L1	2908	DNA	89	NAP1L1	391	Protein
23	OSF-2	3213	DNA	90	OSF-2	836	Protein
24	COL6A3	10558	DNA	91	COL6A3	3176	Protein
25	SPARC	2133	DNA	92	SPARC	303	Protein
26	TGFBI	2691	DNA	93	TGFBI	683	Protein
27	FN1	8027	DNA	94	FN1	2355	Protein
28	COL1A2	5084	DNA	95	COL1A2	1366	Protein
29	S100A11	595	DNA	96	S100A11	105	Protein
30	LC27	2116	DNA	97	LC27	283	Protein
31	IRAK1	3583	DNA	98	IRAK1	712	Protein
32	IFITM2	905	DNA	99	IFITM2	132	Protein
33	TIMP1	782	DNA	100	TIMP1	207	Protein
34	IGFBP7	1124	DNA	101	IGFBP7	282	Protein
35	IFITM1	647	DNA	102	IFITM1	125	Protein
36	COL3A1	5489	DNA	103	COL3A1	1466	Protein

37	IGFBP5	1722	DNA	104	IGFBP5	272	Protein
38	RegIV	1200	DNA	105	RegIV	158	Protein
39	AGR2	1701	DNA	106	AGR2	175	Protein
40	HSPCA	2259	DNA	107	HSPCA	732	Protein
41	KIAA1199	7080	DNA	108	KIAA1199	1361	Protein
42	MMP1	1973	DNA	109	MMP1	469	Protein
43	MMP7	1127	DNA	110	MMP7	267	Protein
44	TSC	1163	DNA	111	TSC	216	Protein
45	HAIK1	2007	DNA	112	HAIK1	422	Protein
46	DAP3	1650	DNA	113	DAP3	398	Protein
47		2566	DNA	114		75	Protein
48		2067	DNA	115		163	Protein
49	KRT8	1752	DNA	116	KRT8	483	Protein
50	KRT18	1412	DNA	117	KRT18	430	Protein
51	KRT19	1407	DNA	118	KRT19	400	Protein
52	KRT20	1723	DNA	119	KRT20	424	Protein
53	MUC1	4139	DNA	120	MUC1	1255	Protein
54	MUC2	15720	DNA	121	MUC2	5179	Protein
55	MUC3	4707	DNA	122	MUC3	1217	Protein
56	MUC5AC	4151	DNA	123	MUC5AC	1373	Protein
57	CGB5	880	DNA	124	CGB5	165	Protein
58	EGFR	5532	DNA	125	EGFR	1210	Protein
59	ERBB2	4530	DNA	126	ERBB2	1255	Protein
60	FTH1	801	DNA	127	FTH1	190	Protein
61	FTL	878	DNA	128	FTL	175	Protein
62	ALPP	2747	DNA	129	ALPP	535	Protein



63	ODC1	2062	DNA	130	ODC1	461	Protein
64	MUC16	3557	DNA	131	MUC16	1148	Protein
65	CEACAM1	3464	DNA	132	CEACAM1	526	Protein
66	CEACAM3	1022	DNA	133	CEACAM3	212	Protein
67	CEACAM4	1190	DNA	134	CEACAM4	244	Protein
68	CEACAM6	2249	DNA	135	CEACAM6	344	Protein
69	CEACAM7	2292	DNA	136	CEACAM7	265	Protein
70	CEACAM8	2297	DNA	137	CEACAM8	349	Protein
71	CA9	1552	DNA	138	CA9	459	Protein

#### Detection Assays

**[0130]** The present invention provides method for detecting colorectal cancer, or alternatively, determining whether a subject is at risk for developing colorectal cancer by detecting the disclosed biomarkers (i.e., the nucleic acid sequence of Reg1 $\alpha$  or TIMP1 and optionally, one or more nucleic acid sequences encoding an additional colorectal cancer associated marker and/or polypeptide markers such as Reg1 $\alpha$  or TIMP1 and optionally, at least one additional colorectal cancer associated marker) for the disease or condition encoded thereby.

**[0131]** In clinical applications, human tissue samples, preferably serum, can be screened for the presence and/or absence of Reg1 $\alpha$  or TIMP1 and/or other colorectal cancer associated markers identified herein. Such samples may comprise tissue samples, whole cells, cell lysates, or isolated nucleic acids, including, for example, needle biopsy cores, surgical resection samples, lymph node tissue, or serum. A sample for analysis as described herein is preferably a serum sample. A serum sample may be obtained from an individual using methods which are well known to those of skill in the art. Briefly, a whole venous or arterial blood sample from an individual is collected into a test tube. The whole blood sample is permitted to incubate at room temperature for approximately 15-30 to allow the blood to clot. Once clotted, the sample is centrifuged at approximately 1500 to 3000 rpm for 5-30 minutes to completely separate the serum from the cellular components. This centrifugation may be repeated if necessary to achieve complete separation. The resulting serum sample may be subsequently screened for the presence of Reg1 $\alpha$  nucleic acid or amino acid and/or one or more additional colorectal cancer associated markers as described herein.

#### Screening for nucleic acid molecules

**[0132]** In one embodiment, the detection method of the present invention comprises determining whether a clinical sample from an individual contains mRNA of a colorectal cancer associated marker, preferably Reg1 $\alpha$  or TIMP1, but also optionally including additional colorectal cancer associated markers as described herein. Techniques for determining the presence of a nucleic acid molecule of interest include Northern blot analysis, reverse transcription-polymerase chain reaction (RT-PCR), in situ hybridization, PCR, and quantitative amplification.

**[0133]** Prior to detection of target nucleic acid molecules in a clinical sample, it is preferred to first isolate the mRNA from the sample to facilitate detection of the target sequence (i.e., a sequence encoding Reg1 $\alpha$  or TIMP1). Methods for isolation of mRNA from a biological sample are well known in the art. Briefly, where the sample is a serum sample, for example, 0.1 ml of 2 M sodium acetate, pH 4, 1 ml water-saturated phenol, and 0.2 ml of 49:1 chloroform/isoamyl alcohol are added to the serum sample sequentially. The sample is mixed after the addition of each component, and incubated for 15 min at 0-4°C after all components have been added. The sample is separated by centrifugation for 20 min at 10,000 x g, 4°C, precipitated by the addition of 1 ml of 100% isopropanol, incubated for 30 minutes at -20°C and pelleted by centrifugation for 10 minutes at 10,000 x g, 4°C. The resulting RNA pellet is dissolved in 0.3 ml denaturing solution, transferred to a microfuge tube, precipitated by the addition of 0.3 ml of 100% isopropanol for 30 minutes

at -20°C, and centrifuged for 10 minutes at 10,000 x g at 4°C. The RNA pellet is washed in 70% ethanol, dried, and resuspended in 100-200µl DEPC-treated water or DEPC-treated 0.5% SDS (Chomczynski and Sacchi, 1987, Anal. Biochem., 162: 156).

[0134] Alternatively, total RNA may be extracted from a clinical sample according to the present invention using a commercially available RNA isolation reagent such as Trizol (Invitrogen, Carlsbad, CA), following the manufacturers instructions. Purity and integrity of RNA is assessed by absorbance at 260/280 nm and separation of RNA samples on a 1% agarose gel followed by inspection under ultraviolet light.

[0135] Following mRNA isolation, the mRNA may be reverse transcribed to provide a cDNA sample according to methods well known to those of skill in the art (see, e.g., Ausubel et al. (1995), Short Protocols in Molecular Biology, 3<sup>rd</sup> Ed. John Wiley and Sons, Inc.)

[0136] Accordingly, in one aspect, the invention provides probes and primers that specifically hybridize to the Reg1α or TIMP1 nucleic acid sequences disclosed herein, or which can hybridize to a nucleic acid molecule encoding an additional colorectal cancer associated marker as described herein. Accordingly, the nucleic acid probes comprise a region of a nucleic acid sequence of SEQ ID Nos 1, 3, or 33 sufficient to hybridize with a nucleic acid substantially complementary to the sequence of SEQ ID Nos 1, 3 or 33. Preferred nucleic acid molecules for use as probes/primers can further comprise a region of nucleic acid sequence substantially complementary to the sequence of SEQ ID Nos. 1, 3 or 33 sufficient to hybridize with the sequence of SEQ ID Nos. 1, 3 or 33. In addition, nucleic acid sequences useful as probes/primers comprise a nucleotide sequence at least about 8 nucleotides in length, at least about 12 nucleotides in length, preferably at least about 15 nucleotides, more preferably about 25 nucleotides, and most preferably at least 40 nucleotides, and up to all or nearly all of the coding sequence which is complementary to a portion of the coding sequence of a marker nucleic acid sequence, which nucleic acid sequence is represented by SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto.

[0137] In one embodiment, the method comprises using a nucleic acid probe to determine the presence of a Reg1α or TIMP1 nucleic acid molecule in a clinical sample (such as a serum sample or a nucleic acid sample extracted therefrom). Specifically, the method comprises:

1. Providing a nucleic acid probe comprising a nucleotide sequence at least about 8 nucleotides in length, at least about 12 nucleotides in length, preferably at least about 15 nucleotides, more preferably about 25 nucleotides, and most preferably at least about 40 nucleotides, and up to all or nearly all of the coding sequence which is complementary to a portion of the coding sequence of a nucleic acid sequence represented by SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto;
2. Obtaining a clinical sample from a patient potentially comprising a Reg1α or TIMP1 nucleic acid sequence;
3. Providing a second clinical sample from an individual known to not have colorectal cancer;
4. Contacting the nucleic acid probe under stringent conditions with RNA of each of said first and second clinical samples (e.g., in a Northern blot or in situ hybridization assay); and
5. Comparing (a) the amount of hybridization of the probe with RNA of the first serum sample, with (b) the amount of hybridization of the probe with RNA of the second clinical sample; wherein a statistically significant difference in the amount of hybridization with the RNA of the first clinical sample as compared to the amount of hybridization with the RNA of the second clinical sample is indicative of the presence of Reg 1α or TIMP1 in the first clinical sample.

[0138] Although, primarily drawn to detection of Reg1α or TIMP1 in a clinical sample such as serum, in one aspect, the present invention provides a method comprising *in situ* hybridization detection of Reg1α or TIMP1 with a probe derived from a nucleic acid sequence represented by SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto. Preferably, the hybridization probe is detectably labeled. The method comprises contacting the labeled hybridization probe with a tissue or cell sample from an individual suspected of having colorectal cancer, washing off any unbound probe, and detecting the signal produced by the detectable label, wherein the detection of the detectable signal is indicative of the presence of Reg1α or TIMP1 in the sample, and thus permits the detection of colorectal cancer. Alternatively, the tissue or cell is additionally hybridized with a detectably labeled nucleic acid probe which is capable of specifically hybridizing with a nucleic acid sequence that encodes at least one additional colorectal cancer associated marker. Detection of the second detectably labeled probe is thus indicative of the presence of the additional colorectal cancer associated marker in the sample, and in conjunction with the detection of Reg1α or TIMP1, permits the detection of colorectal cancer in the individual. Specific methods for *in situ* hybridization are well known in the art.

[0139] Alternatively, methods such as PCR, Northern analysis, and Taqman may be used to detect and/or quantitate

the expression of a nucleic acid sequence encoding Reg1 $\alpha$  in a clinical sample. In one embodiment, reverse transcription PCR (RT-PCR) is performed using primers designed to specifically hybridize to a predetermined portion of the Reg1 $\alpha$  mRNA sequence isolated from a clinical sample. Generation of a PCR product by such a reaction is thus indicative of the presence of the Reg1 $\alpha$  or TIMP1 sequence in the sample. The technique of designing primers for PCR amplification is well known in the art. Oligonucleotide primers and probes are 5 to 100 nucleotides in length, ideally from 17 to 40 nucleotides, although primers and probes of different length are of use. Primers for amplification are preferably about 17-25 nucleotides. Primers useful according to the invention are also designed to have a particular melting temperature ( $T_m$ ) by the method of melting temperature estimation. Commercial programs, including Oligo™ (MBI, Cascade, CO), Primer Design and programs available on the internet, including Primer3 and Oligo Calculator can be used to calculate a  $T_m$  of a nucleic acid sequence useful according to the invention. Preferably, the  $T_m$  of an amplification primer useful according to the invention, as calculated for example by Oligo Calculator, is preferably between about 45 and 65° C and more preferably between about 50 and 60° C. Preferably, the  $T_m$  of a probe useful according to the invention is 7° C higher than the  $T_m$  of the corresponding amplification primers. It is preferred that, following generation of cDNA by RT-PCR, the cDNA fragment is cloned into an appropriate sequencing vector, such as a PCRII vector (TA cloning kit; Invitrogen). The identity of each cloned fragment is then confirmed by sequencing in both directions. It is expected that the sequence obtained from sequencing would be the same as the known sequence of Reg1 $\alpha$  to TIMP1 as described herein.

[0140] Alternatively, the presence of an mRNA sequence encoding Reg1 $\alpha$  or TIMP1 may be detected by Northern analysis. Sequence confirmed cDNAs, that is, cDNAs encoding Reg1 $\alpha$  or TIMP1 (or alternatively an additional colorectal cancer associated marker) are used to produce <sup>32</sup>P-labeled cDNA probes using techniques well known in the art (see, for example, Ausubel, *supra*). Labeled probes for Northern analysis may also be produced using commercially available kits (Prime-It Kit, Stratagene, La Jolla, CA). Northern analysis of total RNA obtained from a clinical sample may be performed using classically described techniques. For example, total RNA samples are denatured with formaldehyde / formamide and run for two hours in a 1 % agarose, MOPS-acetate-EDTA gel. RNA is then transferred to nitrocellulose membrane by upward capillary action and fixed by UV cross-linkage. Membranes are pre-hybridized for at least 90 minutes and hybridized overnight at 42° C. Post hybridization washes are performed as known in the art (Ausubel, *supra*). The membrane is then exposed to x-ray film overnight with an intensifying screen at -80° C. Labeled membranes are then visualized after exposure to film. The signal produced on the x-ray film by the radiolabeled cDNA probes can then be quantified using any technique known in the art, such as scanning the film and quantifying the relative pixel intensity using a computer program such as NIH Image (National Institutes of Health, Bethesda, MD), wherein the detection of hybridization of a Reg1 $\alpha$ -specific probe to the clinical sample is indicative of the presence of Reg1 $\alpha$  or TIMP1 and thus may be used to detect colorectal cancer.

[0141] In an alternate embodiment, the presence and optionally the quantity of Reg1 $\alpha$  or TIMP1 in a clinical sample may be determined using the Taqman™ (Perkin-Elmer, Foster City, CA) technique, which is performed with a transcript-specific antisense probe (i.e., a probe capable of specifically hybridizing to Reg1 $\alpha$ ). This probe is specific for a Reg1 $\alpha$  or TIMP1 PCR product and is prepared with a quencher and fluorescent reporter probe complexed to the 5' end of the oligonucleotide. Different fluorescent markers can be attached to different reporters, allowing for measurement of two products in one reaction (e.g., measurement of Reg1 $\alpha$  or TIMP1 and at least one additional colorectal cancer associated marker). When Taq DNA polymerase is activated, it cleaves off the fluorescent reporters by its 5'-to-3' nucleolytic activity. The reporters, now free of the quenchers, fluoresce. The color change is proportional to the amount of each specific product and is measured by fluorometer; therefore, the amount of each color can be measured and the RT-PCR product can be quantified. The PCR reactions can be performed in 96 well plates so that samples derived from many individuals can be processed and measured simultaneously. The Taqman™ system has the additional advantage of not requiring gel electrophoresis and allows for quantification when used with a standard curve.

#### Screening for polypeptide molecules

[0142] The Reg1 $\alpha$ - or TIMP1-specific and colorectal cancer marker-specific antibodies described above may be used to detect the presence of Reg1 $\alpha$  or TIMP1 or an additional colorectal cancer associated marker in a clinical sample by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitation reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e. g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[0143] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA

buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e. g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e. g., 1-4 hours) at 4 C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4 C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. In the case of immunoprecipitation of a serum sample, however the above protocol is carried out absent the cell lysis step. The ability of the antibody to immunoprecipitate Reg1 $\alpha$  or TIMP 1 (or other colorectal cancer marker) antigen can be assessed by, e. g., western blot analysis. The parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e. g., preclearing the cell lysate with sepharose beads) are well known to those of skill in the art (Ausubel et al, *supra*).

**[0144]** Reg1 $\alpha$  or TIMP1 polypeptides, and optionally one or more additional colorectal cancer associated markers may be detected in a patient clinical sample using Western blot analysis. Briefly, Western blot analysis comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e. g., 8%-20% SDS-PAGE), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e. g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e. g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e. g., an antihuman antibody) conjugated to an enzymatic substrate (e. g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e. g., <sup>32</sup>P or <sup>125</sup>I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. Methods for the optimization of such an analysis are well known in the art (Ausubel, et al., *supra*).

**[0145]** Alternatively, the presence of Reg1 $\alpha$  or TIMP1 and optionally one or more additional colorectal cancer associated markers in a clinical sample may be detected by ELISA. ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate (or other suitable container) with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e. g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest, that is, the antibody which will bind to Reg1 $\alpha$  or TIMP1 or a second colorectal cancer associated marker) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. This method may be modified or optimized according techniques which are known to those of skill in the art.

**[0146]** The binding affinity of an antibody to an antigen and the off-rate of an antibodyantigen interaction can be determined by competitive binding assays. One example of such an assay is a radioimmunoassay comprising the incubation of labeled antigen (e. g., Reg1 $\alpha$  labeled with <sup>3</sup>H or <sup>125</sup>I) with an anti-Reg1 $\alpha$  or TIMP1 antibody in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e. g., <sup>3</sup>H or <sup>125</sup>I) in the presence of increasing amounts of an unlabeled second antibody.

**[0147]** Preferably, the above detection assays re be carried out using antibodies to detect the protein product encoded by a nucleic acid having the sequence of SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto. Preferably, the protein product has the sequence of one or more of SEQ ID Nos. 2, 4, or 100. In addition, the above detection assays may be conducted using one or more antibodies which specifically recognize and bind to at least one additional colorectal cancer associated marker. Accordingly, in one embodiment, the assay would include contacting the proteins of the test cell with an antibody specific for the gene product of a nucleic acid represented by SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto, and determining the approximate amount of immunocomplex formation by the antibody and the proteins of the test cell, wherein a detection of such an immunocomplex is indicative of the presence of the antigen, and thus, permits the detection of colorectal cancer.

**[0148]** Immunoassays, useful in the present invention include those described above, and can also include both homogeneous and heterogeneous procedures such as fluorescence polarization immunoassay (FPIA), fluorescence immunoassay (FIA), enzyme immunoassay (EIA), and nephelometric inhibition immunoassay (NIA).

**[0149]** In another embodiment, the level of the encoded product, i.e., the product encoded by SEQ ID Nos 1, 3 or 33, or a sequence complementary thereto, in a biological fluid (e.g., blood or urine) of a patient may be determined as a way of monitoring the level of expression of the marker nucleic acid sequence in cells of that patient. Such a method would include the steps of obtaining a sample of a biological fluid from the patient, contacting the sample (or proteins from the sample) with an antibody specific for a encoded marker polypeptide, and determining the amount of immune complex formation by the antibody, with the amount of immune complex formation being indicative of the level of the

marker encoded product in the sample. This determination is particularly instructive when compared to the amount of immune complex formation by the same antibody in a control sample taken from a normal individual or in one or more samples previously or subsequently obtained from the same person.

[0150] In another embodiment, the method can be used to determine the amount of marker polypeptide present in a cell, which in turn can be correlated with progression of a hyperproliferative disorder, e.g., colorectal cancer. The level of the marker polypeptide can be used predictively to evaluate whether a sample of cells contains cells which are, or are predisposed towards becoming, transformed cells. Moreover, the subject method can be used to assess the phenotype of cells which are known to be transformed, the phenotyping results being useful in planning a particular therapeutic regimen. For instance, very high levels of the marker polypeptide in sample cells is a powerful diagnostic and prognostic marker for a cancer, such as colorectal cancer. The observation of marker polypeptide level can be utilized in decisions regarding, e.g., the use of more aggressive therapies.

[0151] As set out above, one aspect of the present invention relates to detection assays for determining, in the context of cells isolated from a patient, if the level of a marker polypeptide is significantly reduced in the sample cells. The term "significantly reduced" refers to a cell phenotype wherein the cell possesses a reduced cellular amount of the marker polypeptide relative to a normal cell of similar tissue origin. For example, a cell may have less than about 50%, 25%, 10%, or 5% of the marker polypeptide that a normal control cell. In particular, the assay evaluates the level of marker polypeptide in the test cells, and, preferably, compares the measured level with marker polypeptide detected in at least one control cell, e.g., a normal cell and/or a transformed cell of known phenotype.

[0152] Of particular importance to the subject invention is the ability to quantitate the level of normal or abnormal Reg1 $\alpha$  or TIMP1 expression. The expression of Reg1 $\alpha$  or TIMP1, and/or the level of expression of Reg1 $\alpha$  or TIMP1 can be used predictively to evaluate whether a patient is predisposed towards developing colorectal cancer, or for determining the severity of colorectal cancer.

[0153] In one embodiment, tissue samples may be used to measure Reg1 $\alpha$  or TIMP1 expression by immunohistochemical staining which may be used to determine the number of cells (i.e., colon cells) expressing Reg1 $\alpha$  or TIMP1. For such staining, a multiblock of tissue is taken from the biopsy or other tissue sample and subjected to proteolytic hydrolysis, employing such agents as protease K or pepsin. In certain embodiments, it may be desirable to isolate a nuclear fraction from the sample cells and detect the level of the marker polypeptide in the nuclear fraction.

[0154] The tissue samples are fixed by treatment with a reagent such as formalin, glutaraldehyde, methanol, or the like. The samples are then incubated with an antibody, preferably a monoclonal antibody, with binding specificity for Reg1 $\alpha$  or TIMP1 and optionally an additional colorectal cancer associated marker. This antibody may be conjugated to a label for subsequent detection of binding. Samples are incubated for a time sufficient for formation of the immunocomplexes. Binding of the antibody is then detected by virtue of a label conjugated to this antibody. Where the antibody is unlabeled, a second labeled antibody may be employed, e.g., which is specific for the isotype of the anti-marker polypeptide antibody. Examples of labels which may be employed include radionuclides, fluorescers, chemiluminescers, enzymes and the like.

[0155] Where enzymes are employed, the substrate for the enzyme may be added to the samples to provide a colored or fluorescent product. Examples of suitable enzymes for use in conjugates include horseradish peroxidase, alkaline phosphatase, malate dehydrogenase and the like. Where not commercially available, such antibody-enzyme conjugates are readily produced by techniques known to those skilled in the art. Other assays, known to those of skill in the art for determining the presence and/or quantity of a polypeptide in a sample (either serum or tissue) are also encompassed by the present invention.

#### Drug screening

[0156] Several in vivo methods can be used to identify compounds that modulate expression of Reg1 $\alpha$  or TIMP1 nucleic acids (SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto) and/or alter for example, inhibit the bioactivity of the encoded polypeptide (e.g., SEQ ID Nos: 2, 4, or 100).

[0157] Drug screening is performed by adding a test compound to a sample of cells, and monitoring the effect. A parallel sample which does not receive the test compound is also monitored as a control. The treated and untreated cells are then compared by any suitable phenotypic criteria, including but not limited to microscopic analysis, viability testing, ability to replicate, histological examination, the level of a particular RNA or polypeptide associated with the cells, the level of enzymatic activity expressed by the cells or cell lysates, and the ability of the cells to interact with other cells or compounds. Differences between treated and untreated cells indicates effects attributable to the test compound.

[0158] Desirable effects of a test compound include an effect on any phenotype that was conferred by the cancer-associated marker nucleic acid sequence. Examples include a test compound that limits the overabundance of mRNA, limits production of the encoded protein, or limits the functional effect of the protein. The effect of the test compound would be apparent when comparing results between treated and untreated cells.

**[0159]** The invention thus also encompasses methods of screening for agents which inhibit expression of Reg1 $\alpha$  or TIMP1 nucleic acid (SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto) *in vitro*, comprising exposing either a cell or tissue in which Reg1 $\alpha$  or TIMP1 nucleic acid mRNA is detectable or cultured cells comprising and capable of expressing Reg1 $\alpha$  or TIMP1 nucleic acid to an agent in order to determine whether the agent is capable of inhibiting production of the mRNA; and determining the level of mRNA in the exposed cells or tissue, wherein a decrease in the level of the mRNA after exposure of the cell line to the agent is indicative of inhibition of the marker nucleic acid mRNA production.

**[0160]** Alternatively, the screening method may include *in vitro* screening of a cell or tissue in which Reg1 $\alpha$  or TIMP1 is detectable, or cultured cells which express Reg1 $\alpha$  or TIMP1, to an agent suspected of inhibiting production of Reg1 $\alpha$  or TIMP1 protein; and determining the level of the Reg1 $\alpha$  or TIMP1 protein in the cells or tissue, wherein a decrease in the level of marker protein after exposure of the cells or tissue to the agent is indicative of inhibition of marker protein production.

**[0161]** The invention also encompasses *in vivo* methods of screening for agents which inhibit expression of the marker nucleic acids, comprising exposing a mammal having tumor cells or serum in which Reg1 $\alpha$  or TIMP1 mRNA or protein is detectable to an agent suspected of inhibiting production of marker mRNA or protein; and determining the level of marker mRNA or protein in serum or tumor cells of the exposed mammal. A decrease in the level of marker mRNA or protein after exposure of the mammal to the agent is indicative of inhibition of marker nucleic acid expression. Optionally, the effect of the candidate agent on the expression of at least one additional colorectal cancer associated marker may also be determined.

**[0162]** Accordingly, the invention provides a method comprising incubating a cell expressing the marker nucleic acids (SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto) with a test compound and measuring the mRNA or protein level. The invention further provides a method for quantitatively determining the level of expression of the marker nucleic acids in a cell population or clinical sample, and a method for determining whether an agent is capable of increasing or decreasing the level of expression of the Reg1 $\alpha$  or TIMP1 nucleic acid in a cell population or clinical sample. The method for determining whether an agent is capable of increasing or decreasing the level of expression of Reg1 $\alpha$  or TIMP1 nucleic acid in a cell population comprises the steps of (a) preparing cell extracts from control and agent-treated cell populations, (b) isolating the Reg1 $\alpha$  or TIMP1 polypeptide from the cell extracts, (c) quantifying (e.g., in parallel) the amount of an immunocomplex formed between Reg1 $\alpha$  or TIMP1 polypeptide and an antibody specific to said polypeptide. The Reg1 $\alpha$  or TIMP1 polypeptide of this invention may also be quantified by assaying for its bioactivity. Agents that induce an increase in Reg1 $\alpha$  or TIMP1 nucleic acid expression may be identified by their ability to increase the amount of immunocomplex formed in the treated cell as compared with the amount of the immunocomplex formed in the control cell. In a similar manner, agents that decrease expression of Reg1 $\alpha$  or TIMP1 nucleic acid may be identified by their ability to decrease the amount of the immunocomplex formed in the treated cell extract as compared to the control cell.

**[0163]** mRNA levels can be determined by Northern blot hybridization. mRNA levels can also be determined by methods involving PCR. Other sensitive methods for measuring mRNA, which can be used in high throughput assays, e.g., a method using a DELFIA endpoint detection and quantification method, are described, e.g., in Webb and Hurskainen (1996) *Journal of Biomolecular Screening* 1:119. Reg1 $\alpha$  protein levels can be determined by immunoprecipitations or immunohistochemistry using an antibody that specifically recognizes the protein product of SEQ ID Nos: 2, 4, or 100.

**[0164]** Agents that are identified as active in the drug screening assay are candidates to be tested for their capacity to block cell proliferation activity. These agents would be useful for treating a disorder involving aberrant growth of cells, especially colon cells, especially colorectal cancer.

**[0165]** A variety of assay formats will suffice and, in light of the present disclosure, those not expressly described herein will nevertheless be comprehended by one of ordinary skill in the art. For instance, the assay can be generated in many different formats, and include assays based on cell-free systems, e.g., purified proteins or cell lysates, as well as cell-based assays which utilize intact cells.

**[0166]** In many drug screening programs which test libraries of compounds and natural extracts, high throughput assays are desirable in order to maximize the number of compounds surveyed in a given period of time. Assays of the present invention which are performed in cell-free systems, such as may be derived with purified or semi-purified proteins or with lysates, or with proteins purified or semi-purified from serum, are often preferred as "primary" screens in that they can be generated to permit rapid development and relatively easy detection of an alteration in a molecular target which is mediated by a test compound. Moreover, the effects of cellular toxicity and/or bioavailability of the test compound can be generally ignored in the *in vitro* system, the assay instead being focused primarily on the effect of the drug on the molecular target as may be manifest in an alteration of binding affinity with other proteins or changes in enzymatic properties of the molecular target.

## EXAMPLES

[0167] The examples below are non-limiting and are merely representative of various aspects and features of the present invention.

Example 1: Generation of anti- Reg1 $\alpha$  antibodies

[0168] To generate antibodies to Reg1 $\alpha$ , the full-length open reading frame of Reg1 $\alpha$  (shown in either SEQ ID NO: 1 or 3) was directionally cloned into a mammalian expression vector, such as pcDNA3.1/V5-His (Invitrogen), which includes C-terminal epitope and purification tags. The insert sequence was verified by dideoxy sequencing (see, for example, Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley and Sons). Recombinant fusion protein was produced in a transient expression system in mammalian cells (e.g. CHO cells). The recombinant protein was purified from the cell culture supernatants by immobilized metal affinity chromatography (IMAC) by utilizing the C terminal His-tag. The sequence of the Reg1 $\alpha$  protein used for the production of antibodies of the present invention is shown in either of SEQ ID Nos 2 or 4, all of which represent a functional Reg1 $\alpha$  protein, and which are encoded by SEQ ID Nos 1 or 3, respectively. The purified, recombinant Reg1 $\alpha$  protein was emulsified in Freund's adjuvant and injected into rabbits. The animals were periodically boosted until they elicited a reasonable serum titer of specific antibody to Reg1 $\alpha$ . Methods for antibody production are well known to those of skill in the art and may be found, for example, in Harlow et al. *Antibodies: A laboratory manual*, 1988, Cold Spring Harbor Laboratory. The polyclonal antibodies, which recognized both native and denatured Reg1 $\alpha$ , were utilized to develop a microtiter-based ELISA assay. Methods of performing an ELISA assay are well known to those of skill in the art (see, for example, Ausubel et al., *supra*).

Example 2: Detection of Reg1 $\alpha$  in Colorectal cancer Patient Serum Samples

[0169] The present invention relates to a method for the detection of colorectal cancer in an individual, which method includes the detection of Reg1 $\alpha$  polypeptides in a serum sample from an individual with colorectal cancer, wherein the detection of Reg1 $\alpha$  is indicative of the presence of colorectal cancer. Accordingly, Reg1 $\alpha$  expression was measured in serum samples obtained from patients having been diagnosed with colorectal cancer.

[0170] All patients used in this study were diagnosed at their respective medical institutions by qualified physicians using conventional diagnostic means, including physical exam, blood analysis, imaging, and endoscopy. Once identified, patients provided informed consent through an IRB approved protocol. The severity of colorectal cancer in each patient was graded using the Dukes staging scheme. Serum samples were subsequently collected from each patient using methods known to those of skill in the art. Samples were subsequently assessed for the presence of Reg1 $\alpha$  by the ELISA assay described above. Figure 1 shows the levels of Reg1 $\alpha$  protein measured in the colorectal cancer patients compared to samples obtained from naive patients and additional patients diagnosed with either inflammatory bowel disease (IBD) or cirrhosis of the liver. Figure 2 shows the levels of Reg1 $\alpha$  expression in the colorectal cancer patients of Figure 1, identified at each stage of colorectal cancer severity. As can be seen in Figures 1 and 2, Reg1 $\alpha$  expression is clearly elevated in serum samples obtained from patients diagnosed with colorectal cancer, and therefore may be used to detect the presence of colorectal cancer in a patient.

Example 3: Detection of Reg1 $\alpha$  Nucleic Acid Sequence in Colorectal cancer

[0171] In one embodiment, the present invention provides for a method of detecting the presence of colorectal cancer in a patient by detecting the presence of nucleic acid molecules encoding Reg1 $\alpha$  in a serum sample obtained from a patient.

[0172] Serum may be obtained from a patient suspected of having colorectal cancer by methods described above and known to those of skill in the art. Nucleic acid molecules encoding Reg1 $\alpha$  may be detected, for example, by Northern analysis. Briefly, probes for detection of Reg1 $\alpha$  mRNA in a patient sample are derived by amplifying the Reg1 $\alpha$  coding sequence by RT-PCR according to techniques known in the art. The cDNA fragments generated in this manner are subsequently cloned into a PCRII vector using the TA cloning kit (Invitrogen). The identity of each fragment can be verified by sequencing in each direction from the T3 and T7 polymerase sites present in the cloning vector. The cDNA molecules produced in this manner are then used to produce <sup>32</sup>P-labeled Reg1 $\alpha$  cDNA probes using, for example, the Prime-It kit from Stratagene. Subsequently, 5 to 10  $\mu$ g of total RNA isolated from the serum of a patient suspected of having colorectal cancer is separated on an agarose/formaldehyde gel in 1X MOPS buffer. Methods of isolating RNA from a patient sample such as serum are well known in the art (see, for example, Ausubel et al., *supra*). Following staining with ethidium bromide and visualization under ultra violet light to determine the integrity of the RNA, the RNA is hydrolyzed by treatment with 0.05M NaOH/1.5M NaCl followed by incubation with 0.5M Tris-Cl (pH 7.4)/1.5M NaCl. The RNA is transferred to a commercially available nylon or nitrocellulose membrane (e.g. Hybond-N membrane,

Amersham, Arlington Heights, IL) by methods well known in the art (Ausubel et al., *supra*, Sambrook et al., *supra*). Following transfer and UV cross linking, the membrane is hybridized with a <sup>32</sup>P-labeled Reg1α cDNA probe in hybridization solution (e.g. in 50% formamide/2.5% Denhardt's/100-200mg denatured salmon sperm DNA/0.1% SDS/5X SSPE) overnight at 65°C. The hybridization conditions can be varied as necessary as described in Ausubel et al., *supra* and Sambrook et al., *supra*. Following hybridization, the membrane is washed at room temperature in 2X SSC/0.1% SDS, at 42°C in 1X SSC/0.1% SDS, at 65°C in 0.2X SSC/0.1% SDS, and exposed to film overnight with an intensifying screen at -80° C. The stringency of the wash buffers can also be varied depending on the amount of background signal (Ausubel et al., *supra*). The film is subsequently developed and the intensity bands corresponding to the radiolabeled probe hybridized to RNA are quantified using methods known to those of skill in the art, for example, by digitizing the film and analyzing the band intensity with a computer software program such as NIH Image (NIH, Bethesda, MD).

[0173] Alternatively, Reg1α mRNA may be detected in a patient sample by real-time amplification using oligonucleotide primers capable of specifically hybridizing to the Reg1α sequence. For example, real-time PCR and TaqMan® probes may be used to detect and quantitate the presence of Reg1α mRNA in a patient sample. The technique of real-time PCR is well known in the art (see, for example, U.S. Pat. Nos. 5,691,146; 5,779,977; 5,866,336; and 5,914,230). Methods of designing primers useful for the amplification of Reg1α sequences are well known in the art (see, for example, Ausubel et al., *supra*).

[0174] cDNA samples, reverse transcribed from mRNA obtained from patient serum samples may be used to generate PCR products via an ABI 7700 sequence detection system (Applied Biosystems, Foster City, CA). A measurement may then be made of the level of expression of Reg1α in the patient sample to determine if Reg1α mRNA levels are elevated, thus, providing a means for the detection of colorectal cancer in the patient.

#### Example 4: Detection of Reg1α in Other Patient Samples

[0175] In one embodiment of the present invention, colorectal cancer may be detected in a patient by detecting the expression of Reg1α in a clinical patient sample, which is not a serum sample. For example, a circulating cell sample may be obtained from a patient by collecting a sample such as blood, stool, or other bodily fluid. The sample is then subsequently treated to lyse the cells present therein, for example by treating the sample with a suitable lysis buffer, such as a buffer containing 30 mM Tris-Cl, pH 7.4, 100 mM NaCl, 5 mM EDTA, 1% (w/v) SDS, and 100 μg/ml proteinase K (for isolation of nucleic acid). The resulting sample is then analyzed for Reg1α expression either by isolating total RNA from the sample, as described above, and in Ausubel et al., *supra*, or the sample may be separated on a polyacrylamide gel for analysis by Western blot, or may be utilized in an ELISA-based assay as described above in Example 2.

#### Example 5. Detection of TIMP1 in patient serum samples

[0176] The present invention provides for the detection and monitoring of colorectal cancer in a patient by measuring the level of TIMP 1 polypeptide in a patient sample, preferably in a plasma sample. TIMP 1 expression was determined in 63 samples from patients diagnosed with colorectal cancer relative to the expression level of TIMP1 in 35 healthy individuals. The results demonstrate that TIMP1, in addition to one or more other colorectal cancer associated markers is overexpressed in colorectal cancer samples relative to normal samples, thus indicating that TIMP1 is a valuable marker for the detection of colorectal cancer in a patient (Figure 3).

[0177] To assess TIMP 1 polypeptide expression levels, 63 pre-treatment plasma samples from patients with colorectal cancer, and 35 samples from healthy donors were tested in either commercially available ELISAs (Osteopontin), ADVIA Centaur Immunoassays (CEA and Ferritin), or in-house developed ELISA (TIMP1). All patients used in this study were diagnosed at their respective medical institutions by qualified physicians using conventional diagnostic means, including physical exam, blood analysis, imaging, or endoscopy. Once identified, patients provided informed consent through an IRB approved protocol. The extent of colorectal cancer in each patient was determined using the Dukes' staging scheme. Serum and plasma samples were subsequently collected from each patient using methods known to those of skill in the art.

[0178] Specificity at appropriate cutoff values was determined for each marker (e.g., TIMP1, osteopontin, CEA, and ferritin) by evaluating the normal samples. For example, the 100% specificity cutoff for any given marker is equal to the marker value of the highest normal sample. Using these values as the cutoffs, the levels of each marker in the 63 cancer samples were compared to their own respective cutoff values. If the level in the cancer sample was higher than the determined cutoff value, the sample was deemed "positive" and is represented by a shaded box (Figure 3). This same process was repeated at 97% specificity (using the second highest normal; e.g., 34 of the 35 samples were equal to or below this value). The overall specificity level for the entire panel is calculated by multiplying the specificity of each marker in the panel (e.g., 97% x 97% x 97% x 97% = 89% specificity for the panel). The markers were arranged



on the graphs shown in Figure 3, according to the frequency of their overexpression in the cancer samples (TIMP1 was overexpressed in the highest number of cancer patients and is therefore listed first). The marker adding the most to the sensitivity of TIMP 1 is ranked second. For example, the 57% sensitivity/100% specificity graph shows that TIMP1 was elevated in 19 of the 63 colorectal cancer patient plasma samples, and is thus listed first on the graph.

5 Evaluating the samples for osteopontin yielded seven additional positive patient samples, and osteopontin is thus listed second on the graph.

[0179] The sensitivity of the panel was determined by dividing the cumulative number of samples that were positive for at least one marker by the total number of cancer samples (63). Other embodiments will be evident to those of skill in the art. It should be understood that the foregoing detailed description is provided for clarity only and is merely  
10 exemplary. The spirit and scope of the present invention are not limited to the above examples, but are encompassed by the following claims.

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EP 1 439 393 A2

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atgccacttc cttttaactg ccaagaaatt ttttaaaata aatatttata at  
1552

<210> 72  
 5 <211> 702  
 <212> PRT  
 10 <213> Homo sapiens

<400> 72  
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 1 5 10 15  
 20 Arg Leu Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr  
 20 25 30  
 Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly  
 25 35 40 45  
 Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly  
 50 55 60  
 30 Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Ile  
 65 70 75 80  
 35 Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser  
 85 90 95  
 Gly Arg Glu Ile Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Ile  
 40 100 105 110  
 Ile Gln Asn Asp Thr Gly Phe Tyr Thr Leu His Val Ile Lys Ser Asp  
 45 115 120 125  
 Leu Val Asn Glu Glu Ala Thr Gly Gln Phe Arg Val Tyr Pro Glu Leu  
 130 135 140  
 50 Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Lys Pro Val Glu Asp Lys  
 145 150 155 160  
 55 Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Thr Gln Asp Ala Thr Tyr  
 165 170 175



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Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro Arg Leu Gln  
 180 185 190  
 5 Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Phe Asn Val Thr Arg Asn  
 195 200 205  
 10 Asp Thr Ala Ser Tyr Lys Cys Glu Thr Gln Asn Pro Val Ser Ala Arg  
 210 215 220  
 Arg Ser Asp Ser Val Ile Leu Asn Val Leu Tyr Gly Pro Asp Ala Pro  
 15 225 230 235 240  
 Thr Ile Ser Pro Leu Asn Thr Ser Tyr Arg Ser Gly Glu Asn Leu Asn  
 245 250 255  
 20 Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser Trp Phe  
 260 265 270  
 25 Val Asn Gly Thr Phe Gln Gln Ser Thr Gln Glu Leu Phe Ile Pro Asn  
 275 280 285  
 Ile Thr Val Asn Asn Ser Gly Ser Tyr Thr Cys Gln Ala His Asn Ser  
 30 290 295 300  
 Asp Thr Gly Leu Asn Arg Thr Thr Val Thr Thr Ile Thr Val Tyr Ala  
 35 305 310 315 320  
 Glu Pro Pro Lys Pro Phe Ile Thr Ser Asn Asn Ser Asn Pro Val Glu  
 325 330 335  
 40 Asp Glu Asp Ala Val Ala Leu Thr Cys Glu Pro Glu Ile Gln Asn Thr  
 340 345 350  
 Thr Tyr Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro Arg  
 45 355 360 365  
 Leu Gln Leu Ser Asn Asp Asn Arg Thr Leu Thr Leu Leu Ser Val Thr  
 50 370 375 380  
 Arg Asn Asp Val Gly Pro Tyr Glu Cys Gly Ile Gln Asn Glu Leu Ser  
 385 390 395 400  
 55 Val Asp His Ser Asp Pro Val Ile Leu Asn Val Leu Tyr Gly Pro Asp

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	405	410	415
5	Asp Pro Thr Ile Ser Pro Ser Tyr Thr Tyr Tyr Arg Pro Gly Val Asn		
	420	425	430
	Leu Ser Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser		
10	435	440	445
	Trp Leu Ile Asp Gly Asn Ile Gln Gln His Thr Gln Glu Leu Phe Ile		
	450	455	460
15	Ser Asn Ile Thr Glu Lys Asn Ser Gly Leu Tyr Thr Cys Gln Ala Asn		
	465	470	475
20	Asn Ser Ala Ser Gly His Ser Arg Thr Thr Val Lys Thr Ile Thr Val		
	485	490	495
	Ser Ala Glu Leu Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Lys Pro		
25	500	505	510
	Val Glu Asp Lys Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Ala Gln		
	515	520	525
30	Asn Thr Thr Tyr Leu Trp Trp Val Asn Gly Gln Ser Leu Pro Val Ser		
	530	535	540
35	Pro Arg Leu Gln Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Phe Asn		
	545	550	555
	Val Thr Arg Asn Asp Ala Arg Ala Tyr Val Cys Gly Ile Gln Asn Ser		
40	565	570	575
	Val Ser Ala Asn Arg Ser Asp Pro Val Thr Leu Asp Val Leu Tyr Gly		
45	580	585	590
	Pro Asp Thr Pro Ile Ile Ser Pro Pro Asp Ser Ser Tyr Leu Ser Gly		
	595	600	605
50	Ala Asn Leu Asn Leu Ser Cys His Ser Ala Ser Asn Pro Ser Pro Gln		
	610	615	620
55	Tyr Ser Trp Arg Ile Asn Gly Ile Pro Gln Gln His Thr Gln Val Leu		
	625	630	635
			640

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Phe Ile Ala Lys Ile Thr Pro Asn Asn Asn Gly Thr Tyr Ala Cys Phe  
645 650 655  
5 Val Ser Asn Leu Ala Thr Gly Arg Asn Asn Ser Ile Val Lys Ser Ile  
660 665 670  
10 Thr Val Ser Ala Ser Gly Thr Ser Pro Gly Leu Ser Ala Gly Ala Thr  
675 680 685  
Val Gly Ile Met Ile Gly Val Leu Val Gly Val Ala Leu Ile  
15 690 695 700  
20  
<210> 73  
<211> 609  
25 <212> PRT  
<213> Homo sapiens  
30  
<400> 73  
Met Lys Trp Val Glu Ser Ile Phe Leu Ile Phe Leu Leu Asn Phe Thr  
35 1 5 10 15  
Glu Ser Arg Thr Leu His Arg Asn Glu Tyr Gly Ile Ala Ser Ile Leu  
20 25 30  
40 Asp Ser Tyr Gln Cys Thr Ala Glu Ile Ser Leu Ala Asp Leu Ala Thr  
35 40 45  
45 Ile Phe Phe Ala Gln Phe Val Gln Glu Ala Thr Tyr Lys Glu Val Ser  
50 55 60  
Lys Met Val Lys Asp Ala Leu Thr Ala Ile Glu Lys Pro Thr Gly Asp  
50 65 70 75 80  
Glu Gln Ser Ser Gly Cys Leu Glu Asn Gln Leu Pro Ala Phe Leu Glu  
85 90 95  
55 Glu Leu Cys His Glu Lys Glu Ile Leu Glu Lys Tyr Gly His Ser Asp

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	100	105	110
	Cys Cys Ser Gln Ser Glu Glu Gly Arg His Asn Cys Phe Leu Ala His		
5	115	120	125
	Lys Lys Pro Thr Pro Ala Ser Ile Pro Leu Phe Gln Val Pro Glu Pro		
10	130	135	140
	Val Thr Ser Cys Glu Ala Tyr Glu Glu Asp Arg Glu Thr Phe Met Asn		
	145	150	155
15	Lys Phe Ile Tyr Glu Ile Ala Arg Arg His Pro Phe Leu Tyr Ala Pro		
	165	170	175
	Thr Ile Leu Leu Trp Ala Ala Arg Tyr Asp Lys Ile Ile Pro Ser Cys		
20	180	185	190
	Cys Lys Ala Glu Asn Ala Val Glu Cys Phe Gln Thr Lys Ala Ala Thr		
25	195	200	205
	Val Thr Lys Glu Leu Arg Glu Ser Ser Leu Leu Asn Gln His Ala Cys		
	210	215	220
30	Ala Val Met Lys Asn Phe Gly Thr Arg Thr Phe Gln Ala Ile Thr Val		
	225	230	235
35	Thr Lys Leu Ser Gln Lys Phe Thr Lys Val Asn Phe Thr Glu Ile Gln		
	245	250	255
	Lys Leu Val Leu Asp Val Ala His Val His Glu His Cys Cys Arg Gly		
40	260	265	270
	Asp Val Leu Asp Cys Leu Gln Asp Gly Glu Lys Ile Met Ser Tyr Ile		
	275	280	285
45	Cys Ser Gln Gln Asp Thr Leu Ser Asn Lys Ile Thr Glu Cys Cys Lys		
	290	295	300
50	Leu Thr Thr Leu Glu Arg Gly Gln Cys Ile Ile His Ala Glu Asn Asp		
	305	310	315
	Glu Lys Pro Glu Gly Leu Ser Pro Asn Leu Asn Arg Phe Leu Gly Asp		
55	325	330	335

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Arg Asp Phe Asn Gln Phe Ser Ser Gly Glu Lys Asn Ile Phe Leu Ala  
340 345 350  
5 Ser Phe Val His Glu Tyr Ser Arg Arg His Pro Gln Leu Ala Val Ser  
355 360 365  
10 Val Ile Leu Arg Val Ala Lys Gly Tyr Gln Glu Leu Leu Glu Lys Cys  
370 375 380  
Phe Gln Thr Glu Asn Pro Leu Glu Cys Gln Asp Lys Gly Glu Glu Glu  
15 385 390 395 400  
Leu Gln Lys Tyr Ile Gln Glu Ser Gln Ala Leu Ala Lys Arg Ser Cys  
20 405 410 415  
Gly Leu Phe Gln Lys Leu Gly Glu Tyr Tyr Leu Gln Asn Ala Phe Leu  
420 425 430  
25 Val Ala Tyr Thr Lys Lys Ala Pro Gln Leu Thr Ser Ser Glu Leu Met  
435 440 445  
Ala Ile Thr Arg Lys Met Ala Ala Thr Ala Ala Thr Cys Cys Gln Leu  
30 450 455 460  
Ser Glu Asp Lys Leu Leu Ala Cys Gly Glu Gly Ala Ala Asp Ile Ile  
35 465 470 475 480  
Ile Gly His Leu Cys Ile Arg His Glu Met Thr Pro Val Asn Pro Gly  
485 490 495  
40 Val Gly Gln Cys Cys Thr Ser Ser Tyr Ala Asn Arg Arg Pro Cys Phe  
500 505 510  
45 Ser Ser Leu Val Val Asp Glu Thr Tyr Val Pro Pro Ala Phe Ser Asp  
515 520 525  
Asp Lys Phe Ile Phe His Lys Asp Leu Cys Gln Ala Gln Gly Val Ala  
50 530 535 540  
Leu Gln Thr Met Lys Gln Glu Phe Leu Ile Asn Leu Val Lys Gln Lys  
545 550 555 560  
55 Pro Gln Ile Thr Glu Glu Gln Leu Glu Ala Val Ile Ala Asp Phe Ser

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565 570 575  
 Gly Leu Leu Glu Lys Cys Cys Gln Gly Gln Glu Gln Glu Val Cys Phe  
 5 580 585 590  
 Ala Glu Glu Gly Gln Lys Leu Ile Ser Lys Thr Arg Ala Ala Leu Gly  
 10 595 600 605  
 Val  
 15  
 20 <210> 74  
 <211> 99  
 <212> PRT  
 25 <213> Homo sapiens  
 30 <400> 74  
 Met Thr Ser Lys Leu Ala Val Ala Leu Leu Ala Ala Phe Leu Ile Ser  
 1 5 10 15  
 35 Ala Ala Leu Cys Glu Gly Ala Val Leu Pro Arg Ser Ala Lys Glu Leu  
 20 25 30  
 Arg Cys Gln Cys Ile Lys Thr Tyr Ser Lys Pro Phe His Pro Lys Phe  
 40 35 40 45  
 Ile Lys Glu Leu Arg Val Ile Glu Ser Gly Pro His Cys Ala Asn Thr  
 45 50 55 60  
 Glu Ile Ile Val Lys Leu Ser Asp Gly Arg Glu Leu Cys Leu Asp Pro  
 65 70 75 80  
 50 Lys Glu Asn Trp Val Gln Arg Val Val Glu Lys Phe Leu Lys Arg Ala  
 85 90 95  
 55 Glu Asn Ser

5           <210> 75  
           <211> 300  
 10          <212> PRT  
           <213> Homo sapiens

15           <400> 75  
 Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala  
           1                   5                   10                   15  
 20          Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu  
                   20                   25                   30  
 25          Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro  
                   35                   40                   45  
         Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Thr Leu Pro Ser Lys Ser  
 30           50                   55                   60  
         Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp  
 35          65                   70                   75                   80  
         Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp  
                   85                   90                   95  
 40          Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser  
                   100                   105                   110  
         Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala  
 45           115                   120                   125  
         Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly  
 50           130                   135                   140  
         Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe  
         145                   150                   155                   160  
 55          Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr

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	165	170	175
	Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro		
5	180	185	190
	Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys		
10	195	200	205
	Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His		
	210	215	220
15	Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser		
	225	230	235
20	Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser		
	245	250	255
	Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val		
25	260	265	270
	Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile		
	275	280	285
30	Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn		
	290	295	300
35			
	<210> 76		
40	<211> 871		
	<212> PRT		
45	<213> Homo sapiens		
	<400> 76		
50	Met Lys Tyr Ser Cys Cys Ala Leu Val Leu Ala Val Leu Gly Thr Glu		
	1	5	10
	15		
55	Leu Leu Gly Ser Leu Cys Ser Thr Val Arg Ser Pro Arg Phe Arg Gly		
	20	25	30



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Arg Ile Gln Gln Glu Arg Lys Asn Ile Arg Pro Asn Ile Ile Leu Val  
35 40 45  
5 Leu Thr Asp Asp Gln Asp Val Glu Leu Gly Ser Leu Gln Val Met Asn  
50 55 60  
10 Lys Thr Arg Lys Ile Met Glu His Gly Gly Ala Thr Phe Ile Asn Ala  
65 70 75 80  
Phe Val Thr Thr Pro Met Cys Cys Pro Ser Arg Ser Ser Met Leu Thr  
15 85 90 95  
Gly Lys Tyr Val His Asn His Asn Val Tyr Thr Asn Asn Glu Asn Cys  
100 105 110  
20 Ser Ser Pro Ser Trp Gln Ala Met His Glu Pro Arg Thr Phe Ala Val  
115 120 125  
25 Tyr Leu Asn Asn Thr Gly Tyr Arg Thr Ala Phe Phe Gly Lys Tyr Leu  
130 135 140  
Asn Glu Tyr Asn Gly Ser Tyr Ile Pro Pro Gly Trp Arg Glu Trp Leu  
30 145 150 155 160  
Gly Leu Ile Lys Asn Ser Arg Phe Tyr Asn Tyr Thr Val Cys Arg Asn  
35 165 170 175  
Gly Ile Lys Glu Lys His Gly Phe Asp Tyr Ala Lys Asp Tyr Phe Thr  
180 185 190  
40 Asp Leu Ile Thr Asn Glu Ser Ile Asn Tyr Phe Lys Met Ser Lys Arg  
195 200 205  
45 Met Tyr Pro His Arg Pro Val Met Met Val Ile Ser His Ala Ala Pro  
210 215 220  
His Gly Pro Glu Asp Ser Ala Pro Gln Phe Ser Lys Leu Tyr Pro Asn  
50 225 230 235 240  
Ala Ser Gln His Ile Thr Pro Ser Tyr Asn Tyr Ala Pro Asn Met Asp  
245 250 255  
55 Lys His Trp Ile Met Gln Tyr Thr Gly Pro Met Leu Pro Ile His Met

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	260	265	270
	Glu Phe Thr Asn Ile Leu Gln Arg Lys Arg Leu Gln Thr Leu Met Ser		
5	275	280	285
	Val Asp Asp Ser Val Glu Arg Leu Tyr Asn Met Leu Val Glu Thr Gly		
10	290	295	300
	Glu Leu Glu Asn Thr Tyr Ile Ile Tyr Thr Ala Asp His Gly Tyr His		
	305	310	315
15	Ile Gly Gln Phe Gly Leu Val Lys Gly Lys Ser Met Pro Tyr Asp Phe		
	325	330	335
20	Asp Ile Arg Val Pro Phe Phe Ile Arg Gly Pro Ser Val Glu Pro Gly		
	340	345	350
	Ser Ile Val Pro Gln Ile Val Leu Asn Ile Asp Leu Ala Pro Thr Ile		
25	355	360	365
	Leu Asp Ile Ala Gly Leu Asp Thr Pro Pro Asp Val Asp Gly Lys Ser		
	370	375	380
30	Val Leu Lys Leu Leu Asp Pro Glu Lys Pro Gly Asn Arg Phe Arg Thr		
	385	390	395
35	Asn Lys Lys Ala Lys Ile Trp Arg Asp Thr Phe Leu Val Glu Arg Gly		
	405	410	415
	Lys Phe Leu Arg Lys Lys Glu Glu Ser Ser Lys Asn Ile Gln Gln Ser		
40	420	425	430
	Asn His Leu Pro Lys Tyr Glu Arg Val Lys Glu Leu Cys Gln Gln Ala		
45	435	440	445
	Arg Tyr Gln Thr Ala Cys Glu Gln Pro Gly Gln Lys Trp Gln Cys Ile		
	450	455	460
50	Glu Asp Thr Ser Gly Lys Leu Arg Ile His Lys Cys Lys Gly Pro Ser		
	465	470	475
	Asp Leu Leu Thr Val Arg Gln Ser Thr Arg Asn Leu Tyr Ala Arg Gly		
55	485	490	495

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Phe His Asp Lys Asp Lys Glu Cys Ser Cys Arg Glu Ser Gly Tyr Arg  
500 505 510

5 Ala Ser Arg Ser Gln Arg Lys Ser Gln Arg Gln Phe Leu Arg Asn Gln  
515 520 525

10 Gly Thr Pro Lys Tyr Lys Pro Arg Phe Val His Thr Arg Gln Thr Arg  
530 535 540

Ser Leu Ser Val Glu Phe Glu Gly Glu Ile Tyr Asp Ile Asn Leu Glu  
15 545 550 555 560

Glu Glu Glu Glu Leu Gln Val Leu Gln Pro Arg Asn Ile Ala Lys Arg  
565 570 575

20 His Asp Glu Gly His Lys Gly Pro Arg Asp Leu Gln Ala Ser Ser Gly  
580 585 590

25 Gly Asn Arg Gly Arg Met Leu Ala Asp Ser Ser Asn Ala Val Gly Pro  
595 600 605

Pro Thr Thr Val Arg Val Thr His Lys Cys Phe Ile Leu Pro Asn Asp  
30 610 615 620

Ser Ile His Cys Glu Arg Glu Leu Tyr Gln Ser Ala Arg Ala Trp Lys  
35 625 630 635 640

Asp His Lys Ala Tyr Ile Asp Lys Glu Ile Glu Ala Leu Gln Asp Lys  
645 650 655

40 Ile Lys Asn Leu Arg Glu Val Arg Gly His Leu Lys Arg Arg Lys Pro  
660 665 670

Glu Glu Cys Ser Cys Ser Lys Gln Ser Tyr Tyr Asn Lys Glu Lys Gly  
45 675 680 685

Val Lys Lys Gln Glu Lys Leu Lys Ser His Leu His Pro Phe Lys Glu  
50 690 695 700

Ala Ala Gln Glu Val Asp Ser Lys Leu Gln Leu Phe Lys Glu Asn Asn  
705 710 715 720

55 Arg Arg Arg Lys Lys Glu Arg Lys Glu Lys Arg Arg Gln Arg Lys Gly

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	725	730	735
	Glu Glu Cys Ser Leu Pro Gly Leu Thr Cys Phe Thr His Asp Asn Asn		
5	740	745	750
	His Trp Gln Thr Ala Pro Phe Trp Asn Leu Gly Ser Phe Cys Ala Cys		
10	755	760	765
	Thr Ser Ser Asn Asn Asn Thr Tyr Trp Cys Leu Arg Thr Val Asn Glu		
	770	775	780
15	Thr His Asn Phe Leu Phe Cys Glu Phe Ala Thr Gly Phe Leu Glu Tyr		
	785	790	795 800
20	Phe Asp Met Asn Thr Asp Pro Tyr Gln Leu Thr Asn Thr Val His Thr		
	805	810	815
	Val Glu Arg Gly Ile Leu Asn Gln Leu His Val Gln Leu Met Glu Leu		
25	820	825	830
	Arg Ser Cys Gln Gly Tyr Lys Gln Cys Asn Pro Arg Pro Lys Asn Leu		
	835	840	845
30	Asp Val Gly Asn Lys Asp Gly Gly Ser Tyr Asp Leu His Arg Gly Gln		
	850	855	860
35	Leu Trp Asp Gly Trp Glu Gly		
	865	870	
40			
	<210> 77		
45	<211> 470		
	<212> PRT		
	<213> Homo sapiens		
50			
	<400> 77		
55	Met Lys Phe Leu Leu Ile Leu Leu Leu Gln Ala Thr Ala Ser Gly Ala		
	1	5	10 15

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Leu Pro Leu Asn Ser Ser Thr Ser Leu Glu Lys Asn Asn Val Leu Phe  
 20 25 30  
 5 Gly Glu Arg Tyr Leu Glu Lys Phe Tyr Gly Leu Glu Ile Asn Lys Leu  
 35 40 45  
 10 Pro Val Thr Lys Met Lys Tyr Ser Gly Asn Leu Met Lys Glu Lys Ile  
 50 55 60  
 Gln Glu Met Gln His Phe Leu Gly Leu Lys Val Thr Gly Gln Leu Asp  
 15 65 70 75 80  
 Thr Ser Thr Leu Glu Met Met His Ala Pro Arg Cys Gly Val Pro Asp  
 85 90 95  
 20 Leu His His Phe Arg Glu Met Pro Gly Gly Pro Val Trp Arg Lys His  
 100 105 110  
 25 Tyr Ile Thr Tyr Arg Ile Asn Asn Tyr Thr Pro Asp Met Asn Arg Glu  
 115 120 125  
 Asp Val Asp Tyr Ala Ile Arg Lys Ala Phe Gln Val Trp Ser Asn Val  
 30 130 135 140  
 Thr Pro Leu Lys Phe Ser Lys Ile Asn Thr Gly Met Ala Asp Ile Leu  
 35 145 150 155 160  
 Val Val Phe Ala Arg Gly Ala His Gly Asp Phe His Ala Phe Asp Gly  
 165 170 175  
 40 Lys Gly Gly Ile Leu Ala His Ala Phe Gly Pro Gly Ser Gly Ile Gly  
 180 185 190  
 Gly Asp Ala His Phe Asp Glu Asp Glu Phe Trp Thr Thr His Ser Gly  
 45 195 200 205  
 Gly Thr Asn Leu Phe Leu Thr Ala Val His Glu Ile Gly His Ser Leu  
 50 210 215 220  
 Gly Leu Gly His Ser Ser Asp Pro Lys Ala Val Met Phe Pro Thr Tyr  
 225 230 235 240  
 55 Lys Tyr Val Asp Ile Asn Thr Phe Arg Leu Ser Ala Asp Asp Ile Arg

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	245	250	255
5	Gly Ile Gln Ser Leu Tyr Gly Asp Pro Lys Glu Asn Gln Arg Leu Pro		
	260	265	270
	Asn Pro Asp Asn Ser Glu Pro Ala Leu Cys Asp Pro Asn Leu Ser Phe		
10	275	280	285
	Asp Ala Val Thr Thr Val Gly Asn Lys Ile Phe Phe Phe Lys Asp Arg		
	290	295	300
15	Phe Phe Trp Leu Lys Val Ser Glu Arg Pro Lys Thr Ser Val Asn Leu		
	305	310	315
20	Ile Ser Ser Leu Trp Pro Thr Leu Pro Ser Gly Ile Glu Ala Ala Tyr		
	325	330	335
	Glu Ile Glu Ala Arg Asn Gln Val Phe Leu Phe Lys Asp Asp Lys Tyr		
25	340	345	350
	Trp Leu Ile Ser Asn Leu Arg Pro Glu Pro Asn Tyr Pro Lys Ser Ile		
	355	360	365
30	His Ser Phe Gly Phe Pro Asn Phe Val Lys Lys Ile Asp Ala Ala Val		
	370	375	380
35	Phe Asn Pro Arg Phe Tyr Arg Thr Tyr Phe Phe Val Asp Asn Gln Tyr		
	385	390	395
	Trp Arg Tyr Asp Glu Arg Arg Gln Met Met Asp Pro Gly Tyr Pro Lys		
40	405	410	415
	Leu Ile Thr Lys Asn Phe Gln Gly Ile Gly Pro Lys Ile Asp Ala Val		
45	420	425	430
	Phe Tyr Ser Lys Asn Lys Tyr Tyr Tyr Phe Phe Gln Gly Ser Asn Gln		
	435	440	445
50	Phe Glu Tyr Asp Phe Leu Leu Gln Arg Ile Thr Lys Thr Leu Lys Ser		
	450	455	460
	Asn Ser Trp Phe Gly Cys		
55	465	470	

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       <211> 165  
       <212> PRT  
 10       <213> Homo sapiens

15       <400> 78  
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           1                   5                   10                   15  
 20       Trp Asp Leu Met Thr Phe Asp Ala Asn Pro Tyr Asp Ser Val Lys Lys  
                   20                   25                   30  
 25       Ile Lys Glu His Val Arg Ser Lys Thr Lys Val Pro Val Gln Asp Gln  
                   35                   40                   45  
       Val Leu Leu Leu Gly Ser Lys Ile Leu Lys Pro Arg Arg Ser Leu Ser  
 30           50                   55                   60  
       Ser Tyr Gly Ile Asp Lys Glu Lys Thr Ile His Leu Thr Leu Lys Val  
       65                   70                   75                   80  
 35       Val Lys Pro Ser Asp Glu Glu Leu Pro Leu Phe Leu Val Glu Ser Gly  
                   85                   90                   95  
 40       Asp Glu Ala Lys Arg His Leu Leu Gln Val Arg Arg Ser Ser Ser Val  
                   100                   105                   110  
       Ala Gln Val Lys Ala Met Ile Glu Thr Lys Thr Gly Ile Ile Pro Glu  
 45           115                   120                   125  
       Thr Gln Ile Val Thr Cys Asn Gly Lys Arg Leu Glu Asp Gly Lys Met  
 50           130                   135                   140  
       Met Ala Asp Tyr Gly Ile Arg Lys Gly Asn Leu Leu Phe Leu Ala Ser  
       145                   150                   155                   160  
 55       Tyr Cys Ile Gly Gly

165

5

&lt;210&gt; 79

10

&lt;211&gt; 1464

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

15

&lt;400&gt; 79

20

Met Phe Ser Phe Val Asp Leu Arg Leu Leu Leu Leu Leu Ala Ala Thr

1 5 10 15

Ala Leu Leu Thr His Gly Gln Glu Glu Gly Gln Val Glu Gly Gln Asp

25

20 25 30

Glu Asp Ile Pro Pro Ile Thr Cys Val Gln Asn Gly Leu Arg Tyr His

35 40 45

30

Asp Arg Asp Val Trp Lys Pro Glu Pro Cys Arg Ile Cys Val Cys Asp

50 55 60

35

Asn Gly Lys Val Leu Cys Asp Asp Val Ile Cys Asp Glu Thr Lys Asn

65 70 75 80

Cys Pro Gly Ala Glu Val Pro Glu Gly Glu Cys Cys Pro Val Cys Pro

40

85 90 95

Asp Gly Ser Glu Ser Pro Thr Asp Gln Glu Thr Thr Gly Val Glu Gly

100 105 110

45

Pro Lys Gly Asp Thr Gly Pro Arg Gly Pro Arg Gly Pro Ala Gly Pro

115 120 125

50

Pro Gly Arg Asp Gly Ile Pro Gly Gln Pro Gly Leu Pro Gly Pro Pro

130 135 140

Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala

55

145 150 155 160



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	Pro	Gln	Leu	Ser	Tyr	Gly	Tyr	Asp	Glu	Lys	Ser	Thr	Gly	Gly	Ile	Ser	
						165				170						175	
5	Val	Pro	Gly	Pro	Met	Gly	Pro	Ser	Gly	Pro	Arg	Gly	Leu	Pro	Gly	Pro	
					180				185					190			
10	Pro	Gly	Ala	Pro	Gly	Pro	Gln	Gly	Phe	Gln	Gly	Pro	Pro	Gly	Glu	Pro	
					195			200					205				
	Gly	Glu	Pro	Gly	Ala	Ser	Gly	Pro	Met	Gly	Pro	Arg	Gly	Pro	Pro	Gly	
15		210					215					220					
	Pro	Pro	Gly	Lys	Asn	Gly	Asp	Asp	Gly	Glu	Ala	Gly	Lys	Pro	Gly	Arg	
	225					230					235					240	
20	Pro	Gly	Glu	Arg	Gly	Pro	Pro	Gly	Pro	Gln	Gly	Ala	Arg	Gly	Leu	Pro	
					245				250						255		
25	Gly	Thr	Ala	Gly	Leu	Pro	Gly	Met	Lys	Gly	His	Arg	Gly	Phe	Ser	Gly	
					260				265					270			
	Leu	Asp	Gly	Ala	Lys	Gly	Asp	Ala	Gly	Pro	Ala	Gly	Pro	Lys	Gly	Glu	
30		275						280					285				
	Pro	Gly	Ser	Pro	Gly	Glu	Asn	Gly	Ala	Pro	Gly	Gln	Met	Gly	Pro	Arg	
35		290					295					300					
	Gly	Leu	Pro	Gly	Glu	Arg	Gly	Arg	Pro	Gly	Ala	Pro	Gly	Pro	Ala	Gly	
	305					310					315					320	
40	Ala	Arg	Gly	Asn	Asp	Gly	Ala	Thr	Gly	Ala	Ala	Gly	Pro	Pro	Gly	Pro	
					325					330					335		
45	Thr	Gly	Pro	Ala	Gly	Pro	Pro	Gly	Phe	Pro	Gly	Ala	Val	Gly	Ala	Lys	
					340				345					350			
	Gly	Glu	Ala	Gly	Pro	Gln	Gly	Pro	Arg	Gly	Ser	Glu	Gly	Pro	Gln	Gly	
50		355						360					365				
	Val	Arg	Gly	Glu	Pro	Gly	Pro	Pro	Gly	Pro	Ala	Gly	Ala	Ala	Gly	Pro	
		370					375						380				
55	Ala	Gly	Asn	Pro	Gly	Ala	Asp	Gly	Gln	Pro	Gly	Ala	Lys	Gly	Ala	Asn	

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	385		390		395		400
	Gly Ala Pro Gly Ile Ala Gly Ala Pro Gly Phe Pro Gly Ala Arg Gly						
5			405		410		415
	Pro Ser Gly Pro Gln Gly Pro Gly Gly Pro Pro Gly Pro Lys Gly Asn						
10			420		425		430
	Ser Gly Glu Pro Gly Ala Pro Gly Ser Lys Gly Asp Thr Gly Ala Lys						
			435		440		445
15	Gly Glu Pro Gly Pro Val Gly Val Gln Gly Pro Pro Gly Pro Ala Gly						
			450		455		460
	Glu Glu Gly Lys Arg Gly Ala Arg Gly Glu Pro Gly Pro Thr Gly Leu						
20			465		470		475
							480
	Pro Gly Pro Pro Gly Glu Arg Gly Gly Pro Gly Ser Arg Gly Phe Pro						
25			485		490		495
	Gly Ala Asp Gly Val Ala Gly Pro Lys Gly Pro Ala Gly Glu Arg Gly						
			500		505		510
30	Ser Pro Gly Pro Ala Gly Pro Lys Gly Ser Pro Gly Glu Ala Gly Arg						
			515		520		525
35	Pro Gly Glu Ala Gly Leu Pro Gly Ala Lys Gly Leu Thr Gly Ser Pro						
			530		535		540
	Gly Ser Pro Gly Pro Asp Gly Lys Thr Gly Pro Pro Gly Pro Ala Gly						
40			545		550		555
							560
	Gln Asp Gly Arg Pro Gly Pro Pro Gly Pro Pro Gly Ala Arg Gly Gln						
			565		570		575
45	Ala Gly Val Met Gly Phe Pro Gly Pro Lys Gly Ala Ala Gly Glu Pro						
			580		585		590
50	Gly Lys Ala Gly Glu Arg Gly Val Pro Gly Pro Pro Gly Ala Val Gly						
			595		600		605
	Pro Ala Gly Lys Asp Gly Glu Ala Gly Ala Gln Gly Pro Pro Gly Pro						
55			610		615		620

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Ala Gly Pro Ala Gly Glu Arg Gly Glu Gln Gly Pro Ala Gly Ser Pro  
625 630 635 640

5 Gly Phe Gln Gly Leu Pro Gly Pro Ala Gly Pro Pro Gly Glu Ala Gly  
645 650 655

10 Lys Pro Gly Glu Gln Gly Val Pro Gly Asp Leu Gly Ala Pro Gly Pro  
660 665 670

15 Ser Gly Ala Arg Gly Glu Arg Gly Phe Pro Gly Glu Arg Gly Val Gln  
675 680 685

Gly Pro Pro Gly Pro Ala Gly Pro Arg Gly Ala Asn Gly Ala Pro Gly  
690 695 700

20 Asn Asp Gly Ala Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly Ser  
705 710 715 720

25 Gln Gly Ala Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Ala Ala  
725 730 735

Gly Leu Pro Gly Pro Lys Gly Asp Arg Gly Asp Ala Gly Pro Lys Gly  
740 745 750

30 Ala Asp Gly Ser Pro Gly Lys Asp Gly Val Arg Gly Leu Thr Gly Pro  
755 760 765

35 Ile Gly Pro Pro Gly Pro Ala Gly Ala Pro Gly Asp Lys Gly Glu Ser  
770 775 780

40 Gly Pro Ser Gly Pro Ala Gly Pro Thr Gly Ala Arg Gly Ala Pro Gly  
785 790 795 800

45 Asp Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Phe Ala Gly Pro  
805 810 815

Pro Gly Ala Asp Gly Gln Pro Gly Ala Lys Gly Glu Pro Gly Asp Ala  
820 825 830

50 Gly Ala Lys Gly Asp Ala Gly Pro Pro Gly Pro Ala Gly Pro Ala Gly  
835 840 845

55 Pro Pro Gly Pro Ile Gly Asn Val Gly Ala Pro Gly Ala Lys Gly Ala

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	850	855	860
	Arg Gly Ser Ala Gly Pro Pro Gly Ala Thr Gly Phe Pro Gly Ala Ala		
5	865	870	875 880
	Gly Arg Val Gly Pro Pro Gly Pro Ser Gly Asn Ala Gly Pro Pro Gly		
10	885	890	895
	Pro Pro Gly Pro Ala Gly Lys Glu Gly Gly Lys Gly Pro Arg Gly Glu		
	900	905	910
15	Thr Gly Pro Ala Gly Arg Pro Gly Glu Val Gly Pro Pro Gly Pro Pro		
	915	920	925
	Gly Pro Ala Gly Glu Lys Gly Ser Pro Gly Ala Asp Gly Pro Ala Gly		
20	930	935	940
	Ala Pro Gly Thr Pro Gly Pro Gln Gly Ile Ala Gly Gln Arg Gly Val		
25	945	950	955 960
	Val Gly Leu Pro Gly Gln Arg Gly Glu Arg Gly Phe Pro Gly Leu Pro		
	965	970	975
30	Gly Pro Ser Gly Glu Pro Gly Lys Gln Gly Pro Ser Gly Ala Ser Gly		
	980	985	990
35	Glu Arg Gly Pro Pro Gly Pro Met Gly Pro Pro Gly Leu Ala Gly Pro		
	995	1000	1005
	Pro Gly Glu Ser Gly Arg Glu Gly Ala Pro Ala Ala Glu Gly Ser Pro		
40	1010	1015	1020
	Gly Arg Asp Gly Ser Pro Gly Ala Lys Gly Asp Arg Gly Glu Thr Gly		
45	1025	1030	1035 1040
	Pro Ala Gly Pro Pro Gly Ala Pro Gly Ala Pro Gly Ala Pro Gly Pro		
	1045	1050	1055
50	Val Gly Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu Thr Gly Pro Ala		
	1060	1065	1070
	Gly Pro Ala Gly Pro Val Gly Pro Val Gly Ala Arg Gly Pro Ala Gly		
55	1075	1080	1085

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Pro Gln Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Gln Gly Asp  
1090 1095 1100

5 Arg Gly Ile Lys Gly His Arg Gly Phe Ser Gly Leu Gln Gly Pro Pro  
1105 1110 1115 1120

10 Gly Pro Pro Gly Ser Pro Gly Glu Gln Gly Pro Ser Gly Ala Ser Gly  
1125 1130 1135

Pro Ala Gly Pro Arg Gly Pro Pro Gly Ser Ala Gly Ala Pro Gly Lys  
15 1140 1145 1150

Asp Gly Leu Asn Gly Leu Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg  
1155 1160 1165

20 Gly Arg Thr Gly Asp Ala Gly Pro Val Gly Pro Pro Gly Pro Pro Gly  
1170 1175 1180

25 Pro Pro Gly Pro Pro Gly Pro Pro Ser Ala Gly Phe Asp Phe Ser Phe  
1185 1190 1195 1200

Leu Pro Gln Pro Pro Gln Glu Lys Ala His Asp Gly Gly Arg Tyr Tyr  
30 1205 1210 1215

Arg Ala Asp Asp Ala Asn Val Val Arg Asp Arg Asp Leu Glu Val Asp  
1220 1225 1230

35 Thr Thr Leu Lys Ser Leu Ser Gln Gln Ile Glu Asn Ile Arg Ser Pro  
1235 1240 1245

40 Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Lys Met  
1250 1255 1260

Cys His Ser Asp Trp Lys Ser Gly Glu Tyr Trp Ile Asp Pro Asn Gln  
45 1265 1270 1275 1280

Gly Cys Asn Leu Asp Ala Ile Lys Val Phe Cys Asn Met Glu Thr Gly  
50 1285 1290 1295

Glu Thr Cys Val Tyr Pro Thr Gln Pro Ser Val Ala Gln Lys Asn Trp  
1300 1305 1310

55 Tyr Ile Ser Lys Asn Pro Lys Asp Lys Arg His Val Trp Phe Gly Glu

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	1315	1320	1325
	Ser Met Thr Asp Gly Phe Gln Phe Glu Tyr Gly Gly Gln Gly Ser Asp		
5	1330	1335	1340
	Pro Ala Asp Val Ala Ile Gln Leu Thr Phe Leu Arg Leu Met Ser Thr		
10	1345	1350	1355
	Glu Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Val Ala Tyr		1360
	1365	1370	1375
15	Met Asp Gln Gln Thr Gly Asn Leu Lys Lys Ala Leu Leu Leu Lys Gly		
	1380	1385	1390
20	Ser Asn Glu Ile Glu Ile Arg Ala Glu Gly Asn Ser Arg Phe Thr Tyr		
	1395	1400	1405
	Ser Val Thr Val Asp Gly Cys Thr Ser His Thr Gly Ala Trp Gly Lys		
25	1410	1415	1420
	Thr Val Ile Glu Tyr Lys Thr Thr Lys Ser Ser Arg Leu Pro Ile Ile		
	1425	1430	1435
30	Asp Val Ala Pro Leu Asp Val Gly Ala Pro Asp Gln Glu Phe Gly Phe		1440
	1445	1450	1455
35	Asp Val Gly Pro Val Cys Phe Leu		
	1460		
40			
	<210> 80		
45	<211> 338		
	<212> PRT		
	<213> Homo sapiens		
50			
	<400> 80		
55	Met Ser Leu Ser Ala Phe Thr Leu Phe Leu Ala Leu Ile Gly Gly Thr		
	1	5	10
			15

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Ser Gly Gln Tyr Tyr Asp Tyr Asp Phe Pro Leu Ser Ile Tyr Gly Gln  
20 25 30

5 Ser Ser Pro Asn Cys Ala Pro Glu Cys Asn Cys Pro Glu Ser Tyr Pro  
35 40 45

10 Ser Ala Met Tyr Cys Asp Glu Leu Lys Leu Lys Ser Val Pro Met Val  
50 55 60

Pro Pro Gly Ile Lys Tyr Leu Tyr Leu Arg Asn Asn Gln Ile Asp His  
15 65 70 75 80

Ile Asp Glu Lys Ala Phe Glu Asn Val Thr Asp Leu Gln Trp Leu Ile  
85 90 95

20 Leu Asp His Asn Leu Leu Glu Asn Ser Lys Ile Lys Gly Arg Val Phe  
100 105 110

25 Ser Lys Leu Lys Gln Leu Lys Lys Leu His Ile Asn His Asn Asn Leu  
115 120 125

Thr Glu Ser Val Gly Pro Leu Pro Lys Ser Leu Glu Asp Leu Gln Leu  
30 130 135 140

Thr His Asn Lys Ile Thr Lys Leu Gly Ser Phe Glu Gly Leu Val Asn  
35 145 150 155 160

Leu Thr Phe Ile His Leu Gln His Asn Arg Leu Lys Glu Asp Ala Val  
165 170 175

40 Ser Ala Ala Phe Lys Gly Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser  
180 185 190

Phe Asn Gln Ile Ala Arg Leu Pro Ser Gly Leu Pro Val Ser Leu Leu  
45 195 200 205

Thr Leu Tyr Leu Asp Asn Asn Lys Ile Ser Asn Ile Pro Asp Glu Tyr  
50 210 215 220

Phe Lys Arg Phe Asn Ala Leu Gln Tyr Leu Arg Leu Ser His Asn Glu  
225 230 235 240

55 Leu Ala Asp Ser Gly Ile Pro Gly Asn Ser Phe Asn Val Ser Ser Leu

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245 250 255  
 Val Glu Leu Asp Leu Ser Tyr Asn Lys Leu Lys Asn Ile Pro Thr Val  
 5 260 265 270  
 Asn Glu Asn Leu Glu Asn Tyr Tyr Leu Glu Val Asn Gln Leu Glu Lys  
 10 275 280 285  
 Phe Asp Ile Lys Ser Phe Cys Lys Ile Leu Gly Pro Leu Ser Tyr Ser  
 290 295 300  
 15 Lys Ile Lys His Leu Arg Leu Asp Gly Asn Arg Ile Ser Glu Thr Ser  
 305 310 315 320  
 Leu Pro Pro Asp Met Tyr Glu Cys Leu Arg Val Ala Asn Glu Val Thr  
 20 325 330 335  
 Leu Asn  
 25  
 30 <210> 81  
 <211> 589  
 35 <212> PRT  
 <213> Homo sapiens  
 40 <400> 81  
 Met Ser Val Ser Val His Glu Asn Arg Lys Ser Arg Ala Ser Ser Gly  
 45 1 5 10 15  
 Ser Ile Asn Ile Tyr Leu Phe His Lys Ser Ser Tyr Ala Asp Ser Val  
 20 25 30  
 50 Leu Thr His Leu Asn Leu Leu Arg Gln Gln Arg Leu Phe Thr Asp Val  
 35 40 45  
 Leu Leu His Ala Gly Asn Arg Thr Phe Pro Cys His Arg Ala Val Leu  
 55 50 55 60



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Ala Ala Cys Ser Arg Tyr Phe Glu Ala Met Phe Ser Gly Gly Leu Lys  
65 70 75 80  
5 Glu Ser Gln Asp Ser Glu Val Asn Phe Asp Asn Ser Ile His Pro Glu  
85 90 95  
10 Val Leu Glu Leu Leu Leu Asp Tyr Ala Tyr Ser Ser Arg Val Ile Ile  
100 105 110  
Asn Glu Glu Asn Ala Glu Ser Leu Leu Glu Ala Gly Asp Met Leu Glu  
15 115 120 125  
Phe Gln Asp Ile Arg Asp Ala Cys Ala Glu Phe Leu Glu Lys Asn Leu  
130 135 140  
20 His Pro Thr Asn Cys Leu Gly Met Leu Leu Leu Ser Asp Ala His Gln  
145 150 155 160  
25 Cys Thr Lys Leu Tyr Glu Leu Ser Trp Arg Met Cys Leu Ser Asn Phe  
165 170 175  
Gln Thr Ile Arg Lys Asn Glu Asp Phe Leu Gln Leu Pro Gln Asp Met  
30 180 185 190  
Val Val Gln Leu Leu Ser Ser Glu Glu Leu Glu Thr Glu Asp Glu Arg  
35 195 200 205  
Leu Val Tyr Glu Ser Ala Ile Asn Trp Ile Ser Tyr Asp Leu Lys Lys  
210 215 220  
40 Arg Tyr Cys Tyr Leu Pro Glu Leu Leu Gln Thr Val Arg Leu Ala Leu  
225 230 235 240  
Leu Pro Ala Ile Tyr Leu Met Glu Asn Val Ala Met Glu Glu Leu Ile  
45 245 250 255  
Thr Lys Gln Arg Lys Ser Lys Glu Ile Val Glu Glu Ala Ile Arg Cys  
50 260 265 270  
Lys Leu Lys Ile Leu Gln Asn Asp Gly Val Val Thr Ser Leu Cys Ala  
275 280 285  
55 Arg Pro Arg Lys Thr Gly His Ala Leu Phe Leu Leu Gly Gly Gln Thr

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	290	295	300	
	Phe Met Cys Asp Lys Leu Tyr Leu Val Asp Gln Lys Ala Lys Glu Ile			
5	305	310	315	320
	Ile Pro Lys Ala Asp Ile Pro Ser Pro Arg Lys Glu Phe Ser Ala Cys			
10	325	330	335	
	Ala Ile Gly Cys Lys Val Tyr Ile Thr Gly Gly Arg Gly Ser Glu Asn			
	340	345	350	
15	Gly Val Ser Lys Asp Val Trp Val Tyr Asp Thr Leu His Glu Glu Trp			
	355	360	365	
20	Ser Lys Ala Ala Pro Met Leu Val Ala Arg Phe Gly His Gly Ser Ala			
	370	375	380	
	Glu Leu Lys His Cys Leu Tyr Val Val Gly Gly His Thr Ala Ala Thr			
25	385	390	395	400
	Gly Cys Leu Pro Ala Ser Pro Ser Val Ser Leu Lys Gln Val Glu His			
	405	410	415	
30	Tyr Asp Pro Thr Ile Asn Lys Trp Thr Met Val Ala Pro Leu Arg Glu			
	420	425	430	
35	Gly Val Ser Asn Ala Ala Val Val Ser Ala Lys Leu Lys Leu Phe Ala			
	435	440	445	
	Phe Gly Gly Thr Ser Val Ser His Asp Lys Leu Pro Lys Val Gln Cys			
40	450	455	460	
	Tyr Asp Gln Cys Glu Asn Arg Trp Thr Val Pro Ala Thr Cys Pro Gln			
45	465	470	475	480
	Pro Trp Arg Tyr Thr Ala Ala Ala Val Leu Gly Asn Gln Ile Phe Ile			
	485	490	495	
50	Met Gly Gly Asp Thr Glu Phe Ser Ala Cys Ser Ala Tyr Lys Phe Asn			
	500	505	510	
	Ser Glu Thr Tyr Gln Trp Thr Lys Val Gly Asp Val Thr Ala Lys Arg			
55	515	520	525	

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Met Ser Cys His Ala Val Ala Ser Gly Asn Lys Leu Tyr Val Val Gly  
530 535 540

5 Gly Tyr Phe Gly Ile Gln Arg Cys Lys Thr Leu Asp Cys Tyr Asp Pro  
545 550 555 560

10 Thr Leu Asp Val Trp Asn Ser Ile Thr Thr Val Pro Tyr Ser Leu Ile  
565 570 575

Pro Thr Ala Phe Val Ser Thr Trp Lys His Leu Pro Ser

15 580 585

20 <210> 82  
<211> 193

25 <212> PRT  
<213> Homo sapiens

30 <400> 82

Met Ile Arg Cys Gly Leu Ala Cys Glu Arg Cys Arg Trp Ile Leu Pro  
1 5 10 15

35 Leu Leu Leu Leu Ser Ala Ile Ala Phe Asp Ile Ile Ala Leu Ala Gly  
20 25 30

40 Arg Gly Trp Leu Gln Ser Ser Asp His Gly Gln Thr Ser Ser Leu Trp  
35 40 45

45 Trp Lys Cys Ser Gln Glu Gly Gly Gly Ser Gly Ser Tyr Glu Glu Gly  
50 55 60

Cys Gln Ser Leu Met Glu Tyr Ala Trp Gly Arg Ala Ala Ala Ala Met

50 65 70 75 80

Leu Phe Cys Gly Phe Ile Ile Leu Val Ile Cys Phe Ile Leu Ser Phe

85 90 95

55 Phe Ala Leu Cys Gly Pro Gln Met Leu Val Phe Leu Arg Val Ile Gly

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100 105 110  
 Gly Leu Leu Ala Leu Ala Ala Val Phe Gln Ile Ile Ser Leu Val Ile  
 5 115 120 125  
 Tyr Pro Val Lys Tyr Thr Gln Thr Phe Thr Leu His Ala Asn Pro Ala  
 10 130 135 140  
 Val Thr Tyr Ile Tyr Asn Trp Ala Tyr Gly Phe Gly Trp Ala Ala Thr  
 145 150 155 160  
 15 Ile Ile Leu Ile Gly Cys Ala Phe Phe Phe Cys Cys Leu Leu Asn Tyr  
 165 170 175  
 Glu Asp Asp Leu Leu Gly Asn Ala Lys Pro Arg Tyr Phe Tyr Thr Ser  
 20 180 185 190  
 Ala  
 25  
 30 <210> 83  
 <211> 423  
 <212> PRT  
 35 <213> Homo sapiens  
 40 <400> 83  
 Met Arg Ser Ser Gly Ala Asp Ala Gly Arg Cys Leu Val Thr Ala Arg  
 1 5 10 15  
 45 Ala Pro Gly Ser Val Pro Ala Ser Arg Glu Gly Ser Ala Gly Ser Arg  
 20 25 30  
 50 Gly Pro Gly Ala Arg Phe Pro Ala Arg Val Ser Ala Arg Gly Ser Ala  
 35 40 45  
 Pro Gly Pro Gly Leu Gly Gly Ala Gly Ala Leu Asp Pro Pro Ala Val  
 55 50 55 60

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Val Ala Glu Ser Val Ser Ser Leu Thr Ile Ala Asp Ala Phe Ile Ala  
65 70 75 80  
5 Ala Gly Glu Ser Ser Ala Pro Thr Pro Pro Arg Pro Ala Leu Pro Arg  
85 90 95  
10 Arg Phe Ile Cys Ser Phe Pro Asp Cys Ser Ala Asn Tyr Ser Lys Ala  
100 105 110  
Trp Lys Leu Asp Ala His Leu Cys Lys His Thr Gly Glu Arg Pro Phe  
15 115 120 125  
Val Cys Asp Tyr Glu Gly Cys Gly Lys Ala Phe Ile Arg Asp Tyr His  
130 135 140  
20 Leu Ser Arg His Ile Leu Thr His Thr Gly Glu Lys Pro Phe Val Cys  
145 150 155 160  
25 Ala Ala Asn Gly Cys Asp Gln Lys Phe Asn Thr Lys Ser Asn Leu Lys  
165 170 175  
Lys His Phe Glu Arg Lys His Glu Asn Gln Gln Lys Gln Tyr Ile Cys  
30 180 185 190  
Ser Phe Glu Asp Cys Lys Lys Thr Phe Lys Lys His Gln Gln Leu Lys  
195 200 205  
35 Ile His Gln Cys Gln Asn Thr Asn Glu Pro Leu Phe Lys Cys Thr Gln  
210 215 220  
40 Glu Gly Cys Gly Lys His Phe Ala Ser Pro Ser Lys Leu Lys Arg His  
225 230 235 240  
Ala Lys Ala His Glu Gly Tyr Val Cys Gln Lys Gly Cys Ser Phe Val  
45 245 250 255  
Ala Lys Thr Trp Thr Glu Leu Leu Lys His Val Arg Glu Thr His Lys  
50 260 265 270  
Glu Glu Ile Leu Cys Glu Val Cys Arg Lys Thr Phe Lys Arg Lys Asp  
275 280 285  
55 Tyr Leu Lys Gln His Met Lys Thr His Ala Pro Glu Arg Asp Val Cys

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290 295 300

Arg Cys Pro Arg Glu Gly Cys Gly Arg Thr Tyr Thr Thr Val Phe Asn

5 305 310 315 320

Leu Gln Ser His Ile Leu Ser Phe His Glu Glu Ser Arg Pro Phe Val

10 325 330 335

Cys Glu His Ala Gly Cys Gly Lys Thr Phe Ala Met Lys Gln Ser Leu

340 345 350

15 Thr Arg His Ala Val Val His Asp Pro Asp Lys Lys Lys Met Lys Leu

355 360 365

Lys Val Lys Lys Ser Arg Glu Lys Arg Glu Phe Gly Leu Ser Ser Gln

20 370 375 380

Trp Ile Tyr Pro Pro Lys Arg Lys Gln Gly Gln Gly Leu Ser Leu Cys

25 385 390 395 400

Gln Asn Gly Glu Ser Pro Asn Cys Val Glu Asp Lys Met Leu Ser Thr

405 410 415

30 Val Ala Val Leu Thr Leu Gly

420

35

<210> 84

40 <211> 339

<212> PRT

45 <213> Homo sapiens

<400> 84

50 Met Trp Gln Leu Trp Ala Ser Leu Cys Cys Leu Leu Val Leu Ala Asn

1 5 10 15

Ala Arg Ser Arg Pro Ser Phe His Pro Leu Ser Asp Glu Leu Val Asn

55 20 25 30

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Tyr Val Asn Lys Arg Asn Thr Thr Trp Gln Ala Gly His Asn Phe Tyr  
 35 40 45  
 5 Asn Val Asp Met Ser Tyr Leu Lys Arg Leu Cys Gly Thr Phe Leu Gly  
 50 55 60  
 Gly Pro Lys Pro Pro Gln Arg Val Met Phe Thr Glu Asp Leu Lys Leu  
 10 65 70 75 80  
 Pro Ala Ser Phe Asp Ala Arg Glu Gln Trp Pro Gln Cys Pro Thr Ile  
 15 85 90 95  
 Lys Glu Ile Arg Asp Gln Gly Ser Cys Gly Ser Cys Trp Ala Phe Gly  
 100 105 110  
 20 Ala Val Glu Ala Ile Ser Asp Arg Ile Cys Ile His Thr Asn Ala His  
 115 120 125  
 Val Ser Val Glu Val Ser Ala Glu Asp Leu Leu Thr Cys Cys Gly Ser  
 25 130 135 140  
 Met Cys Gly Asp Gly Cys Asn Gly Gly Tyr Pro Ala Glu Ala Trp Asn  
 30 145 150 155 160  
 Phe Trp Thr Arg Lys Gly Leu Val Ser Gly Gly Leu Tyr Glu Ser His  
 165 170 175  
 35 Val Gly Cys Arg Pro Tyr Ser Ile Pro Pro Cys Glu His His Val Asn  
 180 185 190  
 Gly Ser Arg Pro Pro Cys Thr Gly Glu Gly Asp Thr Pro Lys Cys Ser  
 40 195 200 205  
 Lys Ile Cys Glu Pro Gly Tyr Ser Pro Thr Tyr Lys Gln Asp Lys His  
 45 210 215 220  
 Tyr Gly Tyr Asn Ser Tyr Ser Val Ser Asn Ser Glu Lys Asp Ile Met  
 50 225 230 235 240  
 Ala Glu Ile Tyr Lys Asn Gly Pro Val Glu Gly Ala Phe Ser Val Tyr  
 245 250 255  
 55 Ser Asp Phe Leu Leu Tyr Lys Ser Gly Val Tyr Gln His Val Thr Gly

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260 265 270  
 5 Glu Met Met Gly Gly His Ala Ile Arg Ile Leu Gly Trp Gly Val Glu  
 275 280 285  
 Asn Gly Thr Pro Tyr Trp Leu Val Ala Asn Ser Trp Asn Thr Asp Trp  
 10 290 295 300  
 Gly Asp Asn Gly Phe Phe Lys Ile Leu Arg Gly Gln Asp His Cys Gly  
 305 310 315 320  
 15 Ile Glu Ser Glu Val Val Ala Gly Ile Pro Arg Thr Asp Gln Tyr Trp  
 325 330 335  
 20 Glu Lys Ile  
 25  
 <210> 85  
 <211> 150  
 30 <212> PRT  
 <213> Homo sapiens  
 35  
 <400> 85  
 Met Ala Ala Arg Gly Val Ile Ala Pro Val Gly Glu Ser Leu Arg Tyr  
 40 1 5 10 15  
 Ala Glu Tyr Leu Gln Pro Ser Ala Lys Arg Pro Asp Ala Asp Val Asp  
 45 20 25 30  
 Gln Gln Gly Leu Val Arg Ser Leu Ile Ala Val Gly Leu Gly Val Ala  
 35 40 45  
 50 Ala Leu Ala Phe Ala Gly Arg Tyr Ala Phe Arg Ile Trp Lys Pro Leu  
 50 55 60  
 Glu Gln Val Ile Thr Glu Thr Ala Lys Lys Ile Ser Thr Pro Ser Phe  
 55 65 70 75 80



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Ser Ser Tyr Tyr Lys Gly Gly Phe Glu Gln Lys Met Ser Arg Arg Glu  
5 85 90 95  
Ala Gly Leu Ile Leu Gly Val Ser Pro Ser Ala Gly Lys Ala Lys Ile  
100 105 110  
10 Arg Thr Ala His Arg Arg Val Met Ile Leu Asn His Pro Asp Lys Gly  
115 120 125  
15 Gly Ser Pro Tyr Val Ala Ala Lys Ile Asn Glu Ala Lys Asp Leu Leu  
130 135 140  
Glu Thr Thr Thr Lys His  
20 145 150  
25  
<210> 86  
<211> 1212  
30 <212> PRT  
<213> Homo sapiens  
35  
<400> 86  
Met Glu Pro Arg Pro Thr Ala Pro Ser Ser Gly Ala Pro Gly Leu Ala  
1 5 10 15  
40 Gly Val Gly Glu Thr Pro Ser Ala Ala Ala Leu Ala Ala Ala Arg Val  
20 25 30  
45 Glu Leu Pro Gly Thr Ala Val Pro Ser Val Pro Glu Asp Ala Ala Pro  
35 40 45  
Ala Ser Arg Asp Gly Gly Gly Val Arg Asp Glu Gly Pro Ala Ala Ala  
50 50 55 60  
Gly Asp Gly Leu Gly Arg Pro Leu Gly Pro Thr Pro Ser Gln Ser Arg  
55 65 70 75 80  
Phe Gln Val Asp Leu Val Ser Glu Asn Ala Gly Arg Ala Ala Ala Ala

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	85	90	95
5	Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Gly Ala Gly Ala Gly		
	100	105	110
	Ala Lys Gln Thr Pro Ala Asp Gly Glu Ala Ser Gly Glu Ser Glu Pro		
10	115	120	125
	Ala Lys Gly Ser Glu Glu Ala Lys Gly Arg Phe Arg Val Asn Phe Val		
15	130	135	140
	Asp Pro Ala Ala Ser Ser Ser Ala Glu Asp Ser Leu Ser Asp Ala Ala		
	145	150	155
20	Gly Val Gly Val Asp Gly Pro Asn Val Ser Phe Gln Asn Gly Gly Asp		
	165	170	175
	Thr Val Leu Ser Glu Gly Ser Ser Leu His Ser Gly Gly Gly Gly Gly		
25	180	185	190
	Ser Gly His His Gln His Tyr Tyr Tyr Asp Thr His Thr Asn Thr Tyr		
30	195	200	205
	Tyr Leu Arg Thr Phe Gly His Asn Thr Met Asp Ala Val Pro Arg Ile		
	210	215	220
35	Asp His Tyr Arg His Thr Ala Ala Gln Leu Gly Glu Lys Leu Leu Arg		
	225	230	235
	Pro Ser Leu Ala Glu Leu His Asp Glu Leu Glu Lys Glu Pro Phe Glu		
40	245	250	255
	Asp Gly Phe Ala Asn Gly Glu Glu Ser Thr Pro Thr Arg Asp Ala Val		
45	260	265	270
	Val Thr Tyr Thr Ala Glu Ser Lys Gly Val Val Lys Phe Gly Trp Ile		
	275	280	285
50	Lys Gly Val Leu Val Arg Cys Met Leu Asn Ile Trp Gly Val Met Leu		
	290	295	300
	Phe Ile Arg Leu Ser Trp Ile Val Gly Gln Ala Gly Ile Gly Leu Ser		
55	305	310	315
	320		

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Val Leu Val Ile Met Met Ala Thr Val Val Thr Thr Ile Thr Gly Leu  
5 325 330 335  
Ser Thr Ser Ala Ile Ala Thr Asn Gly Phe Val Arg Gly Gly Gly Ala  
340 345 350  
10 Tyr Tyr Leu Ile Ser Arg Ser Leu Gly Pro Glu Phe Gly Gly Ala Ile  
355 360 365  
Gly Leu Ile Phe Ala Phe Ala Asn Ala Val Ala Val Ala Met Tyr Val  
15 370 375 380  
Val Gly Phe Ala Glu Thr Val Val Glu Leu Leu Lys Glu His Ser Ile  
20 385 390 395 400  
Leu Met Ile Asp Glu Ile Asn Asp Ile Arg Ile Ile Gly Ala Ile Thr  
405 410 415  
25 Val Val Ile Leu Leu Gly Ile Ser Val Ala Gly Met Glu Trp Glu Ala  
420 425 430  
Lys Ala Gln Ile Val Leu Leu Val Ile Leu Leu Leu Ala Ile Gly Asp  
30 435 440 445  
Phe Val Ile Gly Thr Phe Ile Pro Leu Glu Ser Lys Lys Pro Lys Gly  
35 450 455 460  
Phe Phe Gly Tyr Lys Ser Glu Ile Phe Asn Glu Asn Phe Gly Pro Asp  
465 470 475 480  
40 Phe Arg Glu Glu Glu Thr Phe Phe Ser Val Phe Ala Ile Phe Phe Pro  
485 490 495  
45 Ala Ala Thr Gly Ile Leu Ala Gly Ala Asn Ile Ser Gly Asp Leu Ala  
500 505 510  
Asp Pro Gln Ser Ala Ile Pro Lys Gly Thr Leu Leu Ala Ile Leu Ile  
50 515 520 525  
Thr Thr Leu Val Tyr Val Gly Ile Ala Val Ser Val Gly Ser Cys Val  
530 535 540  
55 Val Arg Asp Ala Thr Gly Asn Val Asn Asp Thr Ile Val Thr Glu Leu

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	545	550	555	560
5	Thr Asn Cys Thr Ser Ala Ala Cys Lys Leu Asn Phe Asp Phe Ser Ser			
		565	570	575
	Cys Glu Ser Ser Pro Cys Ser Tyr Gly Leu Met Asn Asn Phe Gln Val			
10		580	585	590
	Met Ser Met Val Ser Gly Phe Thr Pro Leu Ile Ser Ala Gly Ile Phe			
		595	600	605
15	Ser Ala Thr Leu Ser Ser Ala Leu Ala Ser Leu Val Ser Ala Pro Lys			
		610	615	620
20	Ile Phe Gln Ala Leu Cys Lys Asp Asn Ile Tyr Pro Ala Phe Gln Met			
		625	630	635
	Phe Ala Lys Gly Tyr Gly Lys Asn Asn Glu Pro Leu Arg Gly Tyr Ile			
25		645	650	655
	Leu Thr Phe Leu Ile Ala Leu Gly Phe Ile Leu Ile Ala Glu Leu Asn			
		660	665	670
30	Val Ile Ala Pro Ile Ile Ser Asn Phe Phe Leu Ala Ser Tyr Ala Leu			
		675	680	685
35	Ile Asn Phe Ser Val Phe His Ala Ser Leu Ala Lys Ser Pro Gly Trp			
		690	695	700
	Arg Pro Ala Phe Lys Tyr Tyr Asn Met Trp Ile Ser Leu Leu Gly Ala			
40		705	710	715
	Ile Leu Cys Cys Ile Val Met Phe Val Ile Asn Trp Trp Ala Ala Leu			
		725	730	735
45	Leu Thr Tyr Val Ile Val Leu Gly Leu Tyr Ile Tyr Val Thr Tyr Lys			
		740	745	750
50	Lys Pro Asp Val Asn Trp Gly Ser Ser Thr Gln Ala Leu Thr Tyr Leu			
		755	760	765
	Asn Ala Leu Gln His Ser Ile Arg Leu Ser Gly Val Glu Asp His Val			
55		770	775	780

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Lys Asn Phe Arg Pro Gln Cys Leu Val Met Thr Gly Ala Pro Asn Ser  
 5 785 790 795 800  
 Arg Pro Ala Leu Leu His Leu Val His Asp Phe Thr Lys Asn Val Gly  
 805 810 815  
 10 Leu Met Ile Cys Gly His Val His Met Gly Pro Arg Arg Gln Ala Met  
 820 825 830  
 Lys Glu Met Ser Ile Asp Gln Ala Lys Tyr Gln Arg Trp Leu Ile Lys  
 15 835 840 845  
 Asn Lys Met Lys Ala Phe Tyr Ala Pro Val His Ala Asp Asp Leu Arg  
 20 850 855 860  
 Glu Gly Ala Gln Tyr Leu Met Gln Ala Ala Gly Leu Gly Arg Met Lys  
 865 870 875 880  
 25 Pro Asn Thr Leu Val Leu Gly Phe Lys Lys Asp Trp Leu Gln Ala Asp  
 885 890 895  
 Met Arg Asp Val Asp Met Tyr Ile Asn Leu Phe His Asp Ala Phe Asp  
 30 900 905 910  
 Ile Gln Tyr Gly Val Val Val Ile Arg Leu Lys Glu Gly Leu Asp Ile  
 35 915 920 925  
 Ser His Leu Gln Gly Gln Glu Glu Leu Leu Ser Ser Gln Glu Lys Ser  
 930 935 940  
 40 Pro Gly Thr Lys Asp Val Val Val Ser Val Glu Tyr Ser Lys Lys Ser  
 945 950 955 960  
 45 Asp Leu Asp Thr Ser Lys Pro Leu Ser Glu Lys Pro Ile Thr His Lys  
 965 970 975  
 Val Glu Glu Glu Asp Gly Lys Thr Ala Thr Gln Pro Leu Leu Lys Lys  
 50 980 985 990  
 Glu Ser Lys Gly Pro Ile Val Pro Leu Asn Val Ala Asp Gln Lys Leu  
 995 1000 1005  
 55 Leu Glu Ala Ser Thr Gln Phe Gln Lys Lys Gln Gly Lys Asn Thr Ile

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	1010	1015	1020	
5	Asp Val Trp Trp Leu Phe Asp Asp Gly Gly Leu Thr Leu Leu Ile Pro			
	1025	1030	1035	1040
	Tyr Leu Leu Thr Thr Lys Lys Lys Trp Lys Asp Cys Lys Ile Arg Val			
10		1045	1050	1055
	Phe Ile Gly Gly Lys Ile Asn Arg Ile Asp His Asp Arg Arg Ala Met			
	1060	1065	1070	
15	Ala Thr Leu Leu Ser Lys Phe Arg Ile Asp Phe Ser Asp Ile Met Val			
	1075	1080	1085	
20	Leu Gly Asp Ile Asn Thr Lys Pro Lys Lys Glu Asn Ile Ile Ala Phe			
	1090	1095	1100	
	Glu Glu Ile Ile Glu Pro Tyr Arg Leu His Glu Asp Asp Lys Glu Gln			
25	1105	1110	1115	1120
	Asp Ile Ala Asp Lys Met Lys Glu Asp Glu Pro Trp Arg Ile Thr Asp			
	1125	1130	1135	
30	Asn Glu Leu Glu Leu Tyr Lys Thr Lys Thr Tyr Arg Gln Ile Arg Leu			
	1140	1145	1150	
35	Asn Glu Leu Leu Lys Glu His Ser Ser Thr Ala Asn Ile Ile Val Met			
	1155	1160	1165	
	Ser Leu Pro Val Ala Arg Lys Gly Ala Val Ser Ser Ala Leu Tyr Met			
40	1170	1175	1180	
	Ala Trp Leu Glu Ala Leu Ser Lys Asp Leu Pro Pro Ile Leu Leu Val			
45	1185	1190	1195	1200
	Arg Gly Asn His Gln Ser Val Leu Thr Phe Tyr Ser			
	1205	1210		
50				
55	<210> 87			
	<211> 230			

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<212> PRT

<213> Homo sapiens

<400> 87

10 Met Asn Glu Met Tyr Leu Arg Cys Asp His Glu Asn Gln Tyr Ala Gln  
1 5 10 15  
15 Trp Met Ala Ala Cys Met Leu Ala Ser Lys Gly Lys Thr Met Ala Asp  
20 25 30  
Ser Ser Tyr Gln Pro Glu Val Leu Asn Ile Leu Ser Phe Leu Arg Met  
20 35 40 45  
Lys Asn Arg Asn Ser Ala Ser Gln Val Ala Ser Ser Leu Glu Asn Met  
50 55 60  
25 Asp Met Asn Pro Glu Cys Phe Val Ser Pro Arg Cys Ala Lys Arg His  
65 70 75 80  
30 Lys Ser Lys Gln Leu Ala Ala Arg Ile Leu Glu Ala His Gln Asn Val  
85 90 95  
Ala Gln Met Pro Leu Val Glu Ala Lys Leu Arg Phe Ile Gln Ala Trp  
35 100 105 110  
Gln Ser Leu Pro Glu Phe Gly Leu Thr Tyr Tyr Leu Val Arg Phe Lys  
115 120 125  
40 Gly Ser Lys Lys Asp Asp Ile Leu Gly Val Ser Tyr Asn Arg Leu Ile  
130 135 140  
45 Lys Ile Asp Ala Ala Thr Gly Ile Pro Val Thr Thr Trp Arg Phe Thr  
145 150 155 160  
Asn Ile Lys Gln Trp Asn Val Asn Trp Glu Thr Arg Gln Val Val Ile  
50 165 170 175  
Glu Phe Asp Gln Asn Val Phe Thr Ala Phe Thr Cys Leu Ser Ala Asp  
180 185 190  
55 Cys Lys Ile Val His Glu Tyr Ile Gly Gly Tyr Ile Phe Leu Ser Thr

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	195	200	205
5	Arg Ser Lys Asp Gln Asn Glu Thr Leu Asp Glu Asp Leu Phe His Lys		
	210	215	220
	Leu Thr Gly Gly Gln Asp		
10	225	230	
15	<210> 88		
	<211> 383		
20	<212> PRT		
	<213> Homo sapiens		
25	<400> 88		
	Met Glu Ala Leu Gly Lys Leu Lys Gln Phe Asp Ala Tyr Pro Lys Thr		
30	1 5 10 15		
	Leu Glu Asp Phe Arg Val Lys Thr Cys Gly Gly Ala Thr Val Thr Ile		
	20 25 30		
35	Val Ser Gly Leu Leu Met Leu Leu Leu Phe Leu Ser Glu Leu Gln Tyr		
	35 40 45		
	Tyr Leu Thr Thr Glu Val His Pro Glu Leu Tyr Val Asp Lys Ser Arg		
40	50 55 60		
	Gly Asp Lys Leu Lys Ile Asn Ile Asp Val Leu Phe Pro His Met Pro		
45	65 70 75 80		
	Cys Ala Tyr Leu Ser Ile Asp Ala Met Asp Val Ala Gly Glu Gln Gln		
	85 90 95		
50	Leu Asp Val Glu His Asn Leu Phe Lys Gln Arg Leu Asp Lys Asp Gly		
	100 105 110		
	Ile Pro Val Ser Ser Glu Ala Glu Arg His Glu Leu Gly Lys Val Glu		
55	115 120 125		



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Val Thr Val Phe Asp Pro Asp Ser Leu Asp Pro Asp Arg Cys Glu Ser  
5           130                   135                   140  
Cys Tyr Gly Ala Glu Ala Glu Asp Ile Lys Cys Cys Asn Thr Cys Glu  
145                   150                   155                   160  
10 Asp Val Arg Glu Ala Tyr Arg Arg Arg Gly Trp Ala Phe Lys Asn Pro  
                  165                   170                   175  
15 Asp Thr Ile Glu Gln Cys Arg Arg Glu Gly Phe Ser Gln Lys Met Gln  
                  180                   185                   190  
Glu Gln Lys Asn Glu Gly Cys Gln Val Tyr Gly Phe Leu Glu Val Asn  
20           195                   200                   205  
Lys Val Ala Gly Asn Phe His Phe Ala Pro Gly Lys Ser Phe Gln Gln  
                  210                   215                   220  
25 Ser His Val His Val His Asp Leu Gln Ser Phe Gly Leu Asp Asn Ile  
225                   230                   235                   240  
30 Asn Met Thr His Tyr Ile Gln His Leu Ser Phe Gly Glu Asp Tyr Pro  
                  245                   250                   255  
Gly Ile Val Asn Pro Leu Asp His Thr Asn Val Thr Ala Pro Gln Ala  
35           260                   265                   270  
Ser Met Met Phe Gln Tyr Phe Val Lys Val Val Pro Thr Val Tyr Met  
                  275                   280                   285  
40 Lys Val Asp Gly Glu Val Leu Arg Thr Asn Gln Phe Ser Val Thr Arg  
                  290                   295                   300  
45 His Glu Lys Val Ala Asn Gly Leu Leu Gly Asp Gln Gly Leu Pro Gly  
305                   310                   315                   320  
Val Phe Val Leu Tyr Glu Leu Ser Pro Met Met Val Lys Leu Thr Glu  
50                   325                   330                   335  
Lys His Arg Ser Phe Thr His Phe Leu Thr Gly Val Cys Ala Ile Ile  
                  340                   345                   350  
55 Gly Gly Met Phe Thr Val Ala Gly Leu Ile Asp Ser Leu Ile Tyr His

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355 360 365  
 5 Ser Ala Arg Ala Ile Gln Lys Lys Ile Asp Leu Gly Lys Thr Thr  
 370 375 380  
 10  
 <210> 89  
 <211> 391  
 15 <212> PRT  
 <213> Homo sapiens  
 20  
 <400> 89  
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 25 1 5 10 15  
 Asp Asp Val Glu Glu Val Glu Glu Glu Glu Thr Gly Glu Glu Thr Lys  
 30 20 25 30  
 Leu Lys Ala Arg Gln Leu Thr Val Gln Met Met Gln Asn Pro Gln Ile  
 35 35 40 45  
 Leu Ala Ala Leu Gln Glu Arg Leu Asp Gly Leu Val Glu Thr Pro Thr  
 50 55 60  
 Gly Tyr Ile Glu Ser Leu Pro Arg Val Val Lys Arg Arg Val Asn Ala  
 40 65 70 75 80  
 Leu Lys Asn Leu Gln Val Lys Cys Ala Gln Ile Glu Ala Lys Phe Tyr  
 45 85 90 95  
 Glu Glu Val His Asp Leu Glu Arg Lys Tyr Ala Val Leu Tyr Gln Pro  
 100 105 110  
 50 Leu Phe Asp Lys Arg Phe Glu Ile Ile Asn Ala Ile Tyr Glu Pro Thr  
 115 120 125  
 55 Glu Glu Glu Cys Glu Trp Lys Pro Asp Glu Glu Asp Glu Ile Ser Glu  
 130 135 140

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Glu Leu Lys Glu Lys Ala Lys Ile Glu Asp Glu Lys Lys Asp Glu Glu  
 5 145 150 155 160  
 Lys Glu Asp Pro Lys Gly Ile Pro Glu Phe Trp Leu Thr Val Phe Lys  
 165 170 175  
 10 Asn Val Asp Leu Leu Ser Asp Met Val Gln Glu His Asp Glu Pro Ile  
 180 185 190  
 Leu Lys His Leu Lys Asp Ile Lys Val Lys Phe Ser Asp Ala Gly Gln  
 15 195 200 205  
 Pro Met Ser Phe Val Leu Glu Phe His Phe Glu Pro Asn Glu Tyr Phe  
 20 210 215 220  
 Thr Asn Glu Val Leu Thr Lys Thr Tyr Arg Met Arg Ser Glu Pro Asp  
 225 230 235 240  
 25 Asp Ser Asp Pro Phe Ser Phe Asp Gly Pro Glu Ile Met Gly Cys Thr  
 245 250 255  
 Gly Cys Gln Ile Asp Trp Lys Lys Gly Lys Asn Val Thr Leu Lys Thr  
 30 260 265 270  
 Ile Lys Lys Lys Gln Lys His Lys Gly Arg Gly Thr Val Arg Thr Val  
 35 275 280 285  
 Thr Lys Thr Val Ser Asn Asp Ser Phe Phe Asn Phe Phe Ala Pro Pro  
 290 295 300  
 40 Glu Val Pro Glu Ser Gly Asp Leu Asp Asp Asp Ala Glu Ala Ile Leu  
 305 310 315 320  
 Ala Ala Asp Phe Glu Ile Gly His Phe Leu Arg Glu Arg Ile Ile Pro  
 45 325 330 335  
 Arg Ser Val Leu Tyr Phe Thr Gly Glu Ala Ile Glu Asp Asp Asp Asp  
 50 340 345 350  
 Asp Tyr Asp Glu Glu Gly Glu Glu Ala Asp Glu Glu Gly Glu Glu Glu  
 355 360 365  
 55 Gly Asp Glu Glu Asn Asp Pro Asp Tyr Asp Pro Lys Lys Asp Gln Asn

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370 375 380

5 Pro Ala Glu Cys Lys Gln Gln

385 390

10

<210> 90

<211> 836

15 <212> PRT

<213> Homo sapiens

20

<400> 90

Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Leu Ile Val

25 1 5 10 15

Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala His Ser

20 25 30

30 Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln

35 35 40 45

Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr

50 55 60

Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys

40 65 70 75 80

Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu

45 85 90 95

Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr

100 105 110

50 Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly

115 120 125

Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala Trp Asp Asn

55 130 135 140

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	Leu	Asp	Ser	Asp	Ile	Arg	Arg	Gly	Leu	Glu	Ser	Asn	Val	Asn	Val	Glu
5	145					150					155					160
	Leu	Leu	Asn	Ala	Leu	His	Ser	His	Met	Ile	Asn	Lys	Arg	Met	Leu	Thr
					165					170					175	
10	Lys	Asp	Leu	Lys	Asn	Gly	Met	Ile	Ile	Pro	Ser	Met	Tyr	Asn	Asn	Leu
					180					185					190	
	Gly	Leu	Phe	Ile	Asn	His	Tyr	Pro	Asn	Gly	Val	Val	Thr	Val	Asn	Cys
15					195					200					205	
	Ala	Arg	Ile	Ile	His	Gly	Asn	Gln	Ile	Ala	Thr	Asn	Gly	Val	Val	His
20		210				215									220	
	Val	Ile	Asp	Arg	Val	Leu	Thr	Gln	Ile	Gly	Thr	Ser	Ile	Gln	Asp	Phe
	225					230					235				240	
25	Ile	Glu	Ala	Glu	Asp	Asp	Leu	Ser	Ser	Phe	Arg	Ala	Ala	Ala	Ile	Thr
					245					250					255	
	Ser	Asp	Ile	Leu	Glu	Ala	Leu	Gly	Arg	Asp	Gly	His	Phe	Thr	Leu	Phe
30					260					265					270	
	Ala	Pro	Thr	Asn	Glu	Ala	Phe	Glu	Lys	Leu	Pro	Arg	Gly	Val	Leu	Glu
35			275					280						285		
	Arg	Phe	Met	Gly	Asp	Lys	Val	Ala	Ser	Glu	Ala	Leu	Met	Lys	Tyr	His
		290				295						300				
40	Ile	Leu	Asn	Thr	Leu	Gln	Cys	Ser	Glu	Ser	Ile	Met	Gly	Gly	Ala	Val
	305				310						315				320	
45	Phe	Glu	Thr	Leu	Glu	Gly	Asn	Thr	Ile	Glu	Ile	Gly	Cys	Asp	Gly	Asp
					325					330					335	
	Ser	Ile	Thr	Val	Asn	Gly	Ile	Lys	Met	Val	Asn	Lys	Lys	Asp	Ile	Val
50			340					345						350		
	Thr	Asn	Asn	Gly	Val	Ile	His	Leu	Ile	Asp	Gln	Val	Leu	Ile	Pro	Asp
		355				360							365			
55	Ser	Ala	Lys	Gln	Val	Ile	Glu	Leu	Ala	Gly	Lys	Gln	Gln	Thr	Thr	Phe

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	370	375	380	
5	Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu Arg Pro Asp			
	385	390	395	400
	Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe Ser Asp Asp			
10		405	410	415
	Thr Leu Ser Met Val Gln Arg Leu Leu Lys Leu Ile Leu Gln Asn His			
		420	425	430
15	Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn Gly Gln Ile			
		435	440	445
20	Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val Tyr Arg Thr			
		450	455	460
	Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser Lys Gln Gly			
25		465	470	475
	Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys Pro Ala Glu			
		485	490	495
30	Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe Ser Thr Phe			
		500	505	510
35	Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu Thr Gln Pro			
		515	520	525
	Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe Lys Gly Met			
40		530	535	540
	Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn Ala Leu Gln			
45		545	550	555
	Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile Gly Lys Gly			
		565	570	575
50	Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln Gly Ser Lys			
		580	585	590
	Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn Glu Leu Lys			
55		595	600	605

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Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile His Val Val  
5           610                   615                   620  
Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn Asp Gln Leu  
625                   630                   635                   640  
10   Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val  
                  645                   650                   655  
15   Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Thr Thr Lys  
                  660                   665                   670  
Ile Ile Thr Lys Val Val Glu Pro Lys Ile Lys Val Ile Glu Gly Ser  
20           675                   680                   685  
Leu Gln Pro Ile Ile Lys Thr Glu Gly Pro Thr Leu Thr Lys Val Lys  
          690                   695                   700  
25   Ile Glu Gly Glu Pro Glu Phe Arg Leu Ile Lys Glu Gly Glu Thr Ile  
705                   710                   715                   720  
30   Thr Glu Val Ile His Gly Glu Pro Ile Ile Lys Lys Tyr Thr Lys Ile  
                  725                   730                   735  
Ile Asp Gly Val Pro Val Glu Ile Thr Glu Lys Glu Thr Arg Glu Glu  
35           740                   745                   750  
Arg Ile Ile Thr Gly Pro Glu Ile Lys Tyr Thr Arg Ile Ser Thr Gly  
          755                   760                   765  
40   Gly Gly Glu Thr Glu Glu Thr Leu Lys Lys Leu Leu Gln Glu Glu Val  
770                   775                   780  
45   Thr Lys Val Thr Lys Phe Ile Glu Gly Gly Asp Gly His Leu Phe Glu  
785                   790                   795                   800  
Asp Glu Glu Ile Lys Arg Leu Leu Gln Gly Asp Thr Pro Val Arg Lys  
50                   805                   810                   815  
Leu Gln Ala Asn Lys Lys Val Gln Gly Ser Arg Arg Arg Leu Arg Glu  
55           820                   825                   830  
Gly Arg Ser Gln

835

5

&lt;210&gt; 91

10

&lt;211&gt; 3176

&lt;212&gt; PRT

15

&lt;213&gt; Homo sapiens

&lt;400&gt; 91

20

Met Arg Lys His Arg His Leu Pro Leu Val Ala Val Phe Cys Leu Phe

1

5

10

15

Leu Ser Gly Phe Pro Thr Thr His Ala Gln Gln Gln Gln Ala Asp Val

25

20

25

30

Lys Asn Gly Ala Ala Ala Asp Ile Ile Phe Leu Val Asp Ser Ser Trp

30

35

40

45

Thr Ile Gly Glu Glu His Phe Gln Leu Val Arg Glu Phe Leu Tyr Asp

50

55

60

35

Val Val Lys Ser Leu Ala Val Gly Glu Asn Asp Phe His Phe Ala Leu

65

70

75

80

Val Gln Phe Asn Gly Asn Pro His Thr Glu Phe Leu Leu Asn Thr Tyr

40

85

90

95

Arg Thr Lys Gln Glu Val Leu Ser His Ile Ser Asn Met Ser Tyr Ile

45

100

105

110

Gly Gly Thr Asn Gln Thr Gly Lys Gly Leu Glu Tyr Ile Met Gln Ser

115

120

125

50

His Leu Thr Lys Ala Ala Gly Ser Arg Ala Gly Asp Gly Val Pro Gln

130

135

140

Val Ile Val Val Leu Thr Asp Gly His Ser Lys Asp Gly Leu Ala Leu

55

145

150

155

160



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Pro Ser Ala Glu Leu Lys Ser Ala Asp Val Asn Val Phe Ala Ile Gly  
5                                   165                                   170                                   175  
Val Glu Asp Ala Asp Glu Gly Ala Leu Lys Glu Ile Ala Ser Glu Pro  
                                 180                                   185                                   190  
10 Leu Asn Met His Met Phe Asn Leu Glu Asn Phe Thr Ser Leu His Asp  
                                 195                                   200                                   205  
Ile Val Gly Asn Leu Val Ser Cys Val His Ser Ser Val Ser Pro Glu  
15                                   210                                   215                                   220  
Arg Ala Gly Asp Thr Glu Thr Leu Lys Asp Ile Thr Ala Gln Asp Ser  
20                                   225                                   230                                   235                                   240  
Ala Asp Ile Ile Phe Leu Ile Asp Gly Ser Asn Asn Thr Gly Ser Val  
                                 245                                   250                                   255  
25 Asn Phe Ala Val Ile Leu Asp Phe Leu Val Asn Leu Leu Glu Lys Leu  
                                 260                                   265                                   270  
30 Pro Ile Gly Thr Gln Gln Ile Arg Val Gly Val Val Gln Phe Ser Asp  
                                 275                                   280                                   285  
Glu Pro Arg Thr Met Phe Ser Leu Asp Thr Tyr Ser Thr Lys Ala Gln  
35                                   290                                   295                                   300  
Val Leu Gly Ala Val Lys Ala Leu Gly Phe Ala Gly Gly Glu Leu Ala  
                                 305                                   310                                   315                                   320  
40 Asn Ile Gly Leu Ala Leu Asp Phe Val Val Glu Asn His Phe Thr Arg  
                                 325                                   330                                   335  
45 Ala Gly Gly Ser Arg Val Glu Glu Gly Val Pro Gln Val Leu Val Leu  
                                 340                                   345                                   350  
Ile Ser Ala Gly Pro Ser Ser Asp Glu Ile Arg Tyr Gly Val Val Ala  
50                                   355                                   360                                   365  
Leu Lys Gln Ala Ser Val Phe Ser Phe Gly Leu Gly Ala Gln Ala Ala  
                                 370                                   375                                   380  
55 Ser Arg Ala Glu Leu Gln His Ile Ala Thr Asp Asp Asn Leu Val Phe

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	385	390	395	400
5	Thr Val Pro Glu Phe Arg Ser Phe Gly Asp Leu Gln Glu Lys Leu Leu			
		405	410	415
	Pro Tyr Ile Val Gly Val Ala Gln Arg His Ile Val Leu Lys Pro Pro			
10		420	425	430
	Thr Ile Val Thr Gln Val Ile Glu Val Asn Lys Arg Asp Ile Val Phe			
		435	440	445
15	Leu Val Asp Gly Ser Ser Ala Leu Gly Leu Ala Asn Phe Asn Ala Ile			
		450	455	460
20	Arg Asp Phe Ile Ala Lys Val Ile Gln Arg Leu Glu Ile Gly Gln Asp			
		465	470	475
	Leu Ile Gln Val Ala Val Ala Gln Tyr Ala Asp Thr Val Arg Pro Glu			
25		485	490	495
	Phe Tyr Phe Asn Thr His Pro Thr Lys Arg Glu Val Ile Thr Ala Val			
		500	505	510
30	Arg Lys Met Lys Pro Leu Asp Gly Ser Ala Leu Tyr Thr Gly Ser Ala			
		515	520	525
35	Leu Asp Phe Val Arg Asn Asn Leu Phe Thr Ser Ser Ala Gly Tyr Arg			
		530	535	540
	Ala Ala Glu Gly Ile Pro Lys Leu Leu Val Leu Ile Thr Gly Gly Lys			
40		545	550	555
	Ser Leu Asp Glu Ile Ser Gln Pro Ala Gln Glu Leu Lys Arg Ser Ser			
		565	570	575
45	Ile Met Ala Phe Ala Ile Gly Asn Lys Gly Ala Asp Gln Ala Glu Leu			
		580	585	590
50	Glu Glu Ile Ala Phe Asp Ser Ser Leu Val Phe Ile Pro Ala Glu Phe			
		595	600	605
	Arg Ala Ala Pro Leu Gln Gly Met Leu Pro Gly Leu Leu Ala Pro Leu			
55		610	615	620

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Arg Thr Leu Ser Gly Thr Pro Glu Val His Ser Asn Lys Arg Asp Ile  
5 625 630 635 640  
Ile Phe Leu Leu Asp Gly Ser Ala Asn Val Gly Lys Thr Asn Phe Pro  
645 650 655  
10 Tyr Val Arg Asp Phe Val Met Asn Leu Val Asn Ser Leu Asp Ile Gly  
660 665 670  
Asn Asp Asn Ile Arg Val Gly Leu Val Gln Phe Ser Asp Thr Pro Val  
15 675 680 685  
Thr Glu Phe Ser Leu Asn Thr Tyr Gln Thr Lys Ser Asp Ile Leu Gly  
20 690 695 700  
His Leu Arg Gln Leu Gln Leu Gln Gly Gly Ser Gly Leu Asn Thr Gly  
705 710 715 720  
25 Ser Ala Leu Ser Tyr Val Tyr Ala Asn His Phe Thr Glu Ala Gly Gly  
725 730 735  
Ser Arg Ile Arg Glu His Val Pro Gln Leu Leu Leu Leu Leu Thr Ala  
30 740 745 750  
Gly Gln Ser Glu Asp Ser Tyr Leu Gln Ala Ala Asn Ala Leu Thr Arg  
35 755 760 765  
Ala Gly Ile Leu Thr Phe Cys Val Gly Ala Ser Gln Ala Asn Lys Ala  
770 775 780  
40 Glu Leu Glu Gln Ile Ala Phe Asn Pro Ser Leu Val Tyr Leu Met Asp  
785 790 795 800  
45 Asp Phe Ser Ser Leu Pro Ala Leu Pro Gln Gln Leu Ile Gln Pro Leu  
805 810 815  
Thr Thr Tyr Val Ser Gly Gly Val Glu Glu Val Pro Leu Ala Gln Pro  
50 820 825 830  
Glu Ser Lys Arg Asp Ile Leu Phe Leu Phe Asp Gly Ser Ala Asn Leu  
835 840 845  
55 Val Gly Gln Phe Pro Val Val Arg Asp Phe Leu Tyr Lys Ile Ile Asp

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	850	855	860
5	Glu Leu Asn Val Lys Pro Glu Gly Thr Arg Ile Ala Val Ala Gln Tyr		
	865	870	875 880
	Ser Asp Asp Val Lys Val Glu Ser Arg Phe Asp Glu His Gln Ser Lys		
10	885	890	895
	Pro Glu Ile Leu Asn Leu Val Lys Arg Met Lys Ile Lys Thr Gly Lys		
	900	905	910
15	Ala Leu Asn Leu Gly Tyr Ala Leu Asp Tyr Ala Gln Arg Tyr Ile Phe		
	915	920	925
20	Val Lys Ser Ala Gly Ser Arg Ile Glu Asp Gly Val Leu Gln Phe Leu		
	930	935	940
	Val Leu Leu Val Ala Gly Arg Ser Ser Asp Arg Val Asp Gly Pro Ala		
25	945	950	955 960
	Ser Asn Leu Lys Gln Ser Gly Val Val Pro Phe Ile Phe Gln Ala Lys		
	965	970	975
30	Asn Ala Asp Pro Ala Glu Leu Glu Gln Ile Val Leu Ser Pro Ala Phe		
	980	985	990
35	Ile Leu Ala Ala Glu Ser Leu Pro Lys Ile Gly Asp Leu His Pro Gln		
	995	1000	1005
	Ile Val Asn Leu Leu Lys Ser Val His Asn Gly Ala Pro Ala Pro Val		
40	1010	1015	1020
	Ser Gly Glu Lys Asp Val Val Phe Leu Leu Asp Gly Ser Glu Gly Val		
45	1025	1030	1035 1040
	Arg Ser Gly Phe Pro Leu Leu Lys Glu Phe Val Gln Arg Val Val Glu		
	1045	1050	1055
50	Ser Leu Asp Val Gly Gln Asp Arg Val Arg Val Ala Val Val Gln Tyr		
	1060	1065	1070
	Ser Asp Arg Thr Arg Pro Glu Phe Tyr Leu Asn Ser Tyr Met Asn Lys		
55	1075	1080	1085

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Gln Asp Val Val Asn Ala Val Arg Gln Leu Thr Leu Leu Gly Gly Pro  
1090 1095 1100  
5 Thr Pro Asn Thr Gly Ala Ala Leu Glu Phe Val Leu Arg Asn Ile Leu  
1105 1110 1115 1120  
10 Val Ser Ser Ala Gly Ser Arg Ile Thr Glu Gly Val Pro Gln Leu Leu  
1125 1130 1135  
Ile Val Leu Thr Ala Asp Arg Ser Gly Asp Asp Val Arg Asn Pro Ser  
15 1140 1145 1150  
Val Val Val Lys Arg Gly Gly Ala Val Pro Ile Gly Ile Gly Ile Gly  
1155 1160 1165  
20 Asn Ala Asp Ile Thr Glu Met Gln Thr Ile Ser Phe Ile Pro Asp Phe  
1170 1175 1180  
25 Ala Val Ala Ile Pro Thr Phe Arg Gln Leu Gly Thr Val Gln Gln Val  
1185 1190 1195 1200  
Ile Ser Glu Arg Val Thr Gln Leu Thr Arg Glu Glu Leu Ser Arg Leu  
30 1205 1210 1215  
Gln Pro Val Leu Gln Pro Leu Pro Ser Pro Gly Val Gly Gly Lys Arg  
35 1220 1225 1230  
Asp Val Val Phe Leu Ile Asp Gly Ser Gln Ser Ala Gly Pro Glu Phe  
1235 1240 1245  
40 Gln Tyr Val Arg Thr Leu Ile Glu Arg Leu Val Asp Tyr Leu Asp Val  
1250 1255 1260  
45 Gly Phe Asp Thr Thr Arg Val Ala Val Ile Gln Phe Ser Asp Asp Pro  
1265 1270 1275 1280  
Lys Ala Glu Phe Leu Leu Asn Ala His Ser Ser Lys Asp Glu Val Gln  
50 1285 1290 1295  
Asn Ala Val Gln Arg Leu Arg Pro Lys Gly Gly Arg Gln Ile Asn Val  
1300 1305 1310  
55 Gly Asn Ala Leu Glu Tyr Val Ser Arg Asn Ile Phe Lys Arg Pro Leu

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	1315	1320	1325
	Gly Ser Arg Ile Glu Glu Gly Val Pro Gln Phe Leu Val Leu Ile Ser		
5	1330	1335	1340
	Ser Gly Lys Ser Asp Asp Glu Val Val Val Pro Ala Val Glu Leu Lys		
10	1345	1350	1355
	Gln Phe Gly Val Ala Pro Phe Thr Ile Ala Arg Asn Ala Asp Gln Glu		
	1365	1370	1375
15	Glu Leu Val Lys Ile Ser Leu Ser Pro Glu Tyr Val Phe Ser Val Ser		
	1380	1385	1390
20	Thr Phe Arg Glu Leu Pro Ser Leu Glu Gln Lys Leu Leu Thr Pro Ile		
	1395	1400	1405
	Thr Thr Leu Thr Ser Glu Gln Ile Gln Lys Leu Leu Ala Ser Thr Arg		
25	1410	1415	1420
	Tyr Pro Pro Pro Ala Val Glu Ser Asp Ala Ala Asp Ile Val Phe Leu		
	1425	1430	1435
30	Ile Asp Ser Ser Glu Gly Val Arg Pro Asp Gly Phe Ala His Ile Arg		1440
	1445	1450	1455
35	Asp Phe Val Ser Arg Ile Val Arg Arg Leu Asn Ile Gly Pro Ser Lys		
	1460	1465	1470
	Val Arg Val Gly Val Val Gln Phe Ser Asn Asp Val Phe Pro Glu Phe		
40	1475	1480	1485
	Tyr Leu Lys Thr Tyr Arg Ser Gln Ala Pro Val Leu Asp Ala Ile Arg		
45	1490	1495	1500
	Arg Leu Arg Leu Arg Gly Gly Ser Pro Leu Asn Thr Gly Lys Ala Leu		
	1505	1510	1515
50	Glu Phe Val Ala Arg Asn Leu Phe Val Lys Ser Ala Gly Ser Arg Ile		1520
	1525	1530	1535
	Glu Asp Gly Val Pro Gln His Leu Val Leu Val Leu Gly Gly Lys Ser		
55	1540	1545	1550

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	Gln Asp Asp Val Ser Arg Phe Ala Gln Val Ile Arg Ser Ser Gly Ile		
	1555	1560	1565
5	Val Ser Leu Gly Val Gly Asp Arg Asn Ile Asp Arg Thr Glu Leu Gln		
	1570	1575	1580
10	Thr Ile Thr Asn Asp Pro Arg Leu Val Phe Thr Val Arg Glu Phe Arg		
	1585	1590	1595
			1600
	Glu Leu Pro Asn Ile Glu Glu Arg Ile Met Asn Ser Phe Gly Pro Ser		
15		1605	1610
			1615
	Ala Ala Thr Pro Ala Pro Pro Gly Val Asp Thr Pro Pro Pro Ser Arg		
	1620	1625	1630
20	Pro Glu Lys Lys Lys Ala Asp Ile Val Phe Leu Leu Asp Gly Ser Ile		
	1635	1640	1645
25	Asn Phe Arg Arg Asp Ser Phe Gln Glu Val Leu Arg Phe Val Ser Glu		
	1650	1655	1660
	Ile Val Asp Thr Val Tyr Glu Asp Gly Asp Ser Ile Gln Val Gly Leu		
30	1665	1670	1675
			1680
	Val Gln Tyr Asn Ser Asp Pro Thr Asp Glu Phe Phe Leu Lys Asp Phe		
35		1685	1690
			1695
	Ser Thr Lys Arg Gln Ile Ile Asp Ala Ile Asn Lys Val Val Tyr Lys		
	1700	1705	1710
40	Gly Gly Arg His Ala Asn Thr Lys Val Gly Leu Glu His Leu Arg Val		
	1715	1720	1725
45	Asn His Phe Val Pro Glu Ala Gly Ser Arg Leu Asp Gln Arg Val Pro		
	1730	1735	1740
	Gln Ile Ala Phe Val Ile Thr Gly Gly Lys Ser Val Glu Asp Ala Gln		
50	1745	1750	1755
			1760
	Asp Val Ser Leu Ala Leu Thr Gln Arg Gly Val Lys Val Phe Ala Val		
	1765	1770	1775
55	Gly Val Arg Asn Ile Asp Ser Glu Glu Val Gly Lys Ile Ala Ser Asn		

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	1780	1785	1790	
	Ser Ala Thr Ala Phe Arg Val Gly Asn Val Gln Glu Leu Ser Glu Leu			
5	1795	1800	1805	
	Ser Glu Gln Val Leu Glu Thr Leu His Asp Ala Met His Glu Thr Leu			
10	1810	1815	1820	
	Cys Pro Gly Val Thr Asp Ala Ala Lys Ala Cys Asn Leu Asp Val Ile			
	1825	1830	1835	1840
15	Leu Gly Phe Asp Gly Ser Arg Asp Gln Asn Val Phe Val Ala Gln Lys			
	1845	1850	1855	
20	Gly Phe Glu Ser Lys Val Asp Ala Ile Leu Asn Arg Ile Ser Gln Met			
	1860	1865	1870	
	His Arg Val Ser Cys Ser Gly Gly Arg Ser Pro Thr Val Arg Val Ser			
25	1875	1880	1885	
	Val Val Ala Asn Thr Pro Ser Gly Pro Val Glu Ala Phe Asp Phe Asp			
	1890	1895	1900	
30	Glu Tyr Gln Pro Glu Met Leu Glu Lys Phe Arg Asn Met Arg Ser Gln			
	1905	1910	1915	1920
35	His Pro Tyr Val Leu Thr Glu Asp Thr Leu Lys Val Tyr Leu Asn Lys			
	1925	1930	1935	
	Phe Arg Gln Ser Ser Pro Asp Ser Val Lys Val Val Ile His Phe Thr			
40	1940	1945	1950	
	Asp Gly Ala Asp Gly Asp Leu Ala Asp Leu His Arg Ala Ser Glu Asn			
45	1955	1960	1965	
	Leu Arg Gln Glu Gly Val Arg Ala Leu Ile Leu Val Gly Leu Glu Arg			
	1970	1975	1980	
50	Val Val Asn Leu Glu Arg Leu Met His Leu Glu Phe Gly Arg Gly Phe			
	1985	1990	1995	2000
55	Met Tyr Asp Arg Pro Leu Arg Leu Asn Leu Leu Asp Leu Asp Tyr Glu			
	2005	2010	2015	



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	Leu	Ala	Glu	Gln	Leu	Asp	Asn	Ile	Ala	Glu	Lys	Ala	Cys	Cys	Gly	Val
5	Pro	Cys	Lys	Cys	Ser	Gly	Gln	Arg	Gly	Asp	Arg	Gly	Pro	Ile	Gly	Ser
10	Ile	Gly	Pro	Lys	Gly	Ile	Pro	Gly	Glu	Asp	Gly	Tyr	Arg	Gly	Tyr	Pro
15	Gly	Asp	Glu	Gly	Gly	Pro	Gly	Glu	Arg	Gly	Pro	Pro	Gly	Val	Asn	Gly
20	Thr	Gln	Gly	Phe	Gln	Gly	Cys	Pro	Gly	Gln	Arg	Gly	Val	Lys	Gly	Ser
25	Arg	Gly	Phe	Pro	Gly	Glu	Lys	Gly	Glu	Val	Gly	Glu	Ile	Gly	Leu	Asp
30	Gly	Leu	Asp	Gly	Glu	Asp	Gly	Asp	Lys	Gly	Leu	Pro	Gly	Ser	Ser	Gly
35	Glu	Lys	Gly	Asn	Pro	Gly	Arg	Arg	Gly	Asp	Lys	Gly	Pro	Arg	Gly	Glu
40	Lys	Gly	Glu	Arg	Gly	Asp	Val	Gly	Ile	Arg	Gly	Asp	Pro	Gly	Asn	Pro
45	Gly	Gln	Asp	Ser	Gln	Glu	Arg	Gly	Pro	Lys	Gly	Glu	Thr	Gly	Asp	Leu
50	Gly	Pro	Met	Gly	Val	Pro	Gly	Arg	Asp	Gly	Val	Pro	Gly	Gly	Pro	Gly
55	Glu	Thr	Gly	Lys	Asn	Gly	Gly	Phe	Gly	Arg	Arg	Gly	Pro	Pro	Gly	Ala
	Lys	Gly	Asn	Lys	Gly	Gly	Pro	Gly	Gln	Pro	Gly	Phe	Glu	Gly	Glu	Gln
	Gly	Thr	Arg	Gly	Ala	Gln	Gly	Pro	Ala	Gly	Pro	Ala	Gly	Pro	Pro	Gly
	Leu	Ile	Gly	Glu	Gln	Gly	Ile	Ser	Gly	Pro	Arg	Gly	Ser	Gly	Gly	Ala

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	2245	2250	2255
	Arg Gly Ala Pro Gly Glu Arg Gly Arg Thr Gly Pro Leu Gly Arg Lys		
5	2260	2265	2270
	Gly Glu Pro Gly Glu Pro Gly Pro Lys Gly Gly Ile Gly Asn Pro Gly		
10	2275	2280	2285
	Pro Arg Gly Glu Thr Gly Asp Asp Gly Arg Asp Gly Val Gly Ser Glu		
	2290	2295	2300
15	Gly Arg Arg Gly Lys Lys Gly Glu Arg Gly Phe Pro Gly Tyr Pro Gly		
	2305	2310	2315
	Pro Lys Gly Asn Pro Gly Glu Pro Gly Leu Asn Gly Thr Thr Gly Pro		
20	2325	2330	2335
	Lys Gly Ile Arg Gly Arg Arg Gly Asn Ser Gly Pro Pro Gly Ile Val		
25	2340	2345	2350
	Gly Gln Lys Gly Arg Pro Gly Tyr Pro Gly Pro Ala Gly Pro Arg Gly		
	2355	2360	2365
30	Asn Arg Gly Asp Ser Ile Asp Gln Cys Ala Leu Ile Gln Ser Ile Lys		
	2370	2375	2380
35	Asp Lys Cys Pro Cys Cys Tyr Gly Pro Leu Glu Cys Pro Val Phe Pro		
	2385	2390	2395
	Thr Glu Leu Ala Phe Ala Leu Asp Thr Ser Glu Gly Val Asn Gln Asp		
40	2405	2410	2415
	Thr Phe Gly Arg Met Arg Asp Val Val Leu Ser Ile Val Asn Val Leu		
	2420	2425	2430
45	Thr Ile Ala Glu Ser Asn Cys Pro Thr Gly Ala Arg Val Ala Val Val		
	2435	2440	2445
50	Thr Tyr Asn Asn Glu Val Thr Thr Glu Ile Arg Phe Ala Asp Ser Lys		
	2450	2455	2460
	Arg Lys Ser Val Leu Leu Asp Lys Ile Lys Asn Leu Gln Val Ala Leu		
55	2465	2470	2475
	2480		

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	Thr Ser Lys Gln Gln Ser Leu Glu Thr Ala Met Ser Phe Val Ala Arg		
	2485	2490	2495
5	Asn Thr Phe Lys Arg Val Arg Asn Gly Phe Leu Met Arg Lys Val Ala		
	2500	2505	2510
10	Val Phe Phe Ser Asn Thr Pro Thr Arg Ala Ser Pro Gln Leu Arg Glu		
	2515	2520	2525
	Ala Val Leu Lys Leu Ser Asp Ala Gly Ile Thr Pro Leu Phe Leu Thr		
15	2530	2535	2540
	Arg Gln Glu Asp Arg Gln Leu Ile Asn Ala Leu Gln Ile Asn Asn Thr		
	2545	2550	2555
20	Ala Val Gly His Ala Leu Val Leu Pro Ala Gly Arg Asp Leu Thr Asp		
	2565	2570	2575
25	Phe Leu Glu Asn Val Leu Thr Cys His Val Cys Leu Asp Ile Cys Asn		
	2580	2585	2590
	Ile Asp Pro Ser Cys Gly Phe Gly Ser Trp Arg Pro Ser Phe Arg Asp		
30	2595	2600	2605
	Arg Arg Ala Ala Gly Ser Asp Val Asp Ile Asp Met Ala Phe Ile Leu		
	2610	2615	2620
35	Asp Ser Ala Glu Thr Thr Thr Leu Phe Gln Phe Asn Glu Met Lys Lys		
	2625	2630	2635
			2640
40	Tyr Ile Ala Tyr Leu Val Arg Gln Leu Asp Met Ser Pro Asp Pro Lys		
	2645	2650	2655
	Ala Ser Gln His Phe Ala Arg Val Ala Val Val Gln His Ala Pro Ser		
45	2660	2665	2670
	Glu Ser Val Asp Asn Ala Ser Met Pro Pro Val Lys Val Glu Phe Ser		
	2675	2680	2685
50	Leu Thr Asp Tyr Gly Ser Lys Glu Lys Leu Val Asp Phe Leu Ser Arg		
	2690	2695	2700
55	Gly Met Thr Gln Leu Gln Gly Thr Arg Ala Leu Gly Ser Ala Ile Glu		

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	2705	2710	2715	2720
	Tyr Thr Ile Glu Asn Val Phe Glu Ser Ala Pro Asn Pro Arg Asp Leu			
5		2725	2730	2735
	Lys Ile Val Val Leu Met Leu Thr Gly Glu Val Pro Glu Gln Gln Leu			
10		2740	2745	2750
	Glu Glu Ala Gln Arg Val Ile Leu Gln Ala Lys Cys Lys Gly Tyr Phe			
	2755	2760	2765	
15	Phe Val Val Leu Gly Ile Gly Arg Lys Val Asn Ile Lys Glu Val Tyr			
	2770	2775	2780	
20	Thr Phe Ala Ser Glu Pro Asn Asp Val Phe Phe Lys Leu Val Asp Lys			
	2785	2790	2795	2800
	Ser Thr Glu Leu Asn Glu Glu Pro Leu Met Arg Phe Gly Arg Leu Leu			
25		2805	2810	2815
	Pro Ser Phe Val Ser Ser Glu Asn Ala Phe Tyr Leu Ser Pro Asp Ile			
	2820	2825	2830	
30	Arg Lys Gln Cys Asp Trp Phe Gln Gly Asp Gln Pro Thr Lys Asn Leu			
	2835	2840	2845	
35	Val Lys Phe Gly His Lys Gln Val Asn Val Pro Asn Asn Val Thr Ser			
	2850	2855	2860	
	Ser Pro Thr Ser Asn Pro Val Thr Thr Thr Lys Pro Val Thr Thr Thr			
40	2865	2870	2875	2880
	Lys Pro Val Thr Thr Thr Thr Lys Pro Val Thr Thr Thr Lys Pro			
45		2885	2890	2895
	Val Thr Ile Ile Asn Gln Pro Ser Val Lys Pro Ala Ala Ala Lys Pro			
	2900	2905	2910	
50	Ala Pro Ala Lys Pro Val Ala Ala Lys Pro Val Ala Thr Lys Thr Ala			
	2915	2920	2925	
	Thr Val Arg Pro Pro Val Ala Val Lys Pro Ala Thr Ala Ala Lys Pro			
55	2930	2935	2940	

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Val Ala Ala Lys Pro Ala Ala Val Arg Pro Pro Ala Ala Ala Lys  
2945 2950 2955 2960  
5 Pro Val Ala Thr Lys Pro Glu Val Pro Arg Pro Gln Ala Ala Lys Pro  
2965 2970 2975  
10 Ala Ala Thr Lys Pro Ala Thr Thr Lys Pro Val Val Lys Met Leu Arg  
2980 2985 2990  
Glu Val Gln Val Phe Glu Ile Thr Glu Asn Ser Ala Lys Leu His Trp  
15 2995 3000 3005  
Glu Arg Pro Glu Pro Pro Gly Pro Tyr Phe Tyr Asp Leu Thr Val Thr  
20 3010 3015 3020  
Ser Ala His Asp Gln Ser Leu Val Leu Lys Gln Asn Leu Thr Val Thr  
3025 3030 3035 3040  
25 Asp Arg Val Ile Gly Gly Leu Leu Ala Gly Gln Thr Tyr His Val Ala  
3045 3050 3055  
Val Val Cys Tyr Leu Arg Ser Gln Val Arg Ala Thr Tyr His Gly Ser  
30 3060 3065 3070  
Phe Ser Thr Lys Lys Ser Gln Pro Pro Pro Pro Gln Pro Ala Arg Ser  
35 3075 3080 3085  
Ala Ser Ser Ser Thr Ile Asn Leu Met Val Ser Thr Glu Pro Leu Ala  
3090 3095 3100  
40 Leu Thr Glu Thr Asp Ile Cys Lys Leu Pro Lys Asp Glu Gly Thr Cys  
3105 3110 3115 3120  
45 Arg Asp Phe Ile Leu Lys Trp Tyr Tyr Asp Pro Asn Thr Lys Ser Cys  
3125 3130 3135  
Ala Arg Phe Trp Tyr Gly Gly Cys Gly Gly Asn Glu Asn Lys Phe Gly  
50 3140 3145 3150  
Ser Gln Lys Glu Cys Glu Lys Val Cys Ala Pro Val Leu Ala Lys Pro  
3155 3160 3165  
55 Gly Val Ile Ser Val Met Gly Thr

3170 3175

5

<210> 92

10 <211> 303

<212> PRT

<213> Homo sapiens

15

<400> 92

20 Met Arg Ala Trp Ile Phe Phe Leu Leu Cys Leu Ala Gly Arg Ala Leu

1 5 10 15

Ala Ala Pro Gln Gln Glu Ala Leu Pro Asp Glu Thr Glu Val Val Glu

25 20 25 30

Glu Thr Val Ala Glu Val Thr Glu Val Ser Val Gly Ala Asn Pro Val

30 35 40 45

Gln Val Glu Val Gly Glu Phe Asp Asp Gly Ala Glu Glu Thr Glu Glu

50 55 60

35 Glu Val Val Ala Glu Asn Pro Cys Gln Asn His His Cys Lys His Gly

65 70 75 80

Lys Val Cys Glu Leu Asp Glu Asn Asn Thr Pro Met Cys Val Cys Gln

40 85 90 95

Asp Pro Thr Ser Cys Pro Ala Pro Ile Gly Glu Phe Glu Lys Val Cys

45 100 105 110

Ser Asn Asp Asn Lys Thr Phe Asp Ser Ser Cys His Phe Phe Ala Thr

115 120 125

50 Lys Cys Thr Leu Glu Gly Thr Lys Lys Gly His Lys Leu His Leu Asp

130 135 140

55 Tyr Ile Gly Pro Cys Lys Tyr Ile Pro Pro Cys Leu Asp Ser Glu Leu

145 150 155 160

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Thr Glu Phe Pro Leu Arg Met Arg Asp Trp Leu Lys Asn Val Leu Val  
165 170 175  
5 Thr Leu Tyr Glu Arg Asp Glu Asp Asn Asn Leu Leu Thr Glu Lys Gln  
180 185 190  
10 Lys Leu Arg Val Lys Lys Ile His Glu Asn Glu Lys Arg Leu Glu Ala  
195 200 205  
Gly Asp His Pro Val Glu Leu Leu Ala Arg Asp Phe Glu Lys Asn Tyr  
15 210 215 220  
Asn Met Tyr Ile Phe Pro Val His Trp Gln Phe Gly Gln Leu Asp Gln  
225 230 235 240  
20 His Pro Ile Asp Gly Tyr Leu Ser His Thr Glu Leu Ala Pro Leu Arg  
245 250 255  
25 Ala Pro Leu Ile Pro Met Glu His Cys Thr Thr Arg Phe Phe Glu Thr  
260 265 270  
Cys Asp Leu Asp Asn Asp Lys Tyr Ile Ala Leu Asp Glu Trp Ala Gly  
30 275 280 285  
Cys Phe Gly Ile Lys Gln Lys Asp Ile Asp Lys Asp Leu Val Ile  
35 290 295 300  
40 <210> 93  
<211> 683  
45 <212> PRT  
<213> Homo sapiens  
50 <400> 93  
Met Ala Leu Phe Val Arg Leu Leu Ala Leu Ala Leu Ala Leu Ala Leu  
1 5 10 15  
55 Gly Pro Ala Ala Thr Leu Ala Gly Pro Ala Lys Ser Pro Tyr Gln Leu

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	20	25	30
	Val Leu Gln His Ser Arg Leu Arg Gly Arg Gln His Gly Pro Asn Val		
5	35	40	45
	Cys Ala Val Gln Lys Val Ile Gly Thr Asn Arg Lys Tyr Phe Thr Asn		
10	50	55	60
	Cys Lys Gln Trp Tyr Gln Arg Lys Ile Cys Gly Lys Ser Thr Val Ile		
	65	70	75
15	80		
	Ser Tyr Glu Cys Cys Pro Gly Tyr Glu Lys Val Pro Gly Glu Lys Gly		
	85	90	95
20			
	Cys Pro Ala Ala Leu Pro Leu Ser Asn Leu Tyr Glu Thr Leu Gly Val		
	100	105	110
	Val Gly Ser Thr Thr Thr Gln Leu Tyr Thr Asp Arg Thr Glu Lys Leu		
25	115	120	125
	Arg Pro Glu Met Glu Gly Pro Gly Ser Phe Thr Ile Phe Ala Pro Ser		
	130	135	140
30			
	Asn Glu Ala Trp Ala Ser Leu Pro Ala Glu Val Leu Asp Ser Leu Val		
	145	150	155
35	160		
	Ser Asn Val Asn Ile Glu Leu Leu Asn Ala Leu Arg Tyr His Met Val		
	165	170	175
	Gly Arg Arg Val Leu Thr Asp Glu Leu Lys His Gly Met Thr Leu Thr		
40	180	185	190
	Ser Met Tyr Gln Asn Ser Asn Ile Gln Ile His His Tyr Pro Asn Gly		
45	195	200	205
	Ile Val Thr Val Asn Cys Ala Arg Leu Leu Lys Ala Asp His His Ala		
	210	215	220
50			
	Thr Asn Gly Val Val His Leu Ile Asp Lys Val Ile Ser Thr Ile Thr		
	225	230	235
55	240		
	Asn Asn Ile Gln Gln Ile Ile Glu Ile Glu Asp Thr Phe Glu Thr Leu		
	245	250	255



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Arg Ala Ala Val Ala Ala Ser Gly Leu Asn Thr Met Leu Glu Gly Asn  
260 265 270  
5 Gly Gln Tyr Thr Leu Leu Ala Pro Thr Asn Glu Ala Phe Glu Lys Ile  
275 280 285  
10 Pro Ser Glu Thr Leu Asn Arg Ile Leu Gly Asp Pro Glu Ala Leu Arg  
290 295 300  
Asp Leu Leu Asn Asn His Ile Leu Lys Ser Ala Met Cys Ala Glu Ala  
15 305 310 315 320  
Ile Val Ala Gly Leu Ser Val Glu Thr Leu Glu Gly Thr Thr Leu Glu  
20 325 330 335  
Val Gly Cys Ser Gly Asp Met Leu Thr Ile Asn Gly Lys Ala Ile Ile  
340 345 350  
25 Ser Asn Lys Asp Ile Leu Ala Thr Asn Gly Val Ile His Tyr Ile Asp  
355 360 365  
Glu Leu Leu Ile Pro Asp Ser Ala Lys Thr Leu Phe Glu Leu Ala Ala  
30 370 375 380  
Glu Ser Asp Val Ser Thr Ala Ile Asp Leu Phe Arg Gln Ala Gly Leu  
35 385 390 395 400  
Gly Asn His Leu Ser Gly Ser Glu Arg Leu Thr Leu Leu Ala Pro Leu  
405 410 415  
40 Asn Ser Val Phe Lys Asp Gly Thr Pro Pro Ile Asp Ala His Thr Arg  
420 425 430  
45 Asn Leu Leu Arg Asn His Ile Ile Lys Asp Gln Leu Ala Ser Lys Tyr  
435 440 445  
Leu Tyr His Gly Gln Thr Leu Glu Thr Leu Gly Gly Lys Lys Leu Arg  
50 450 455 460  
Val Phe Val Tyr Arg Asn Ser Leu Cys Ile Glu Asn Ser Cys Ile Ala  
55 465 470 475 480  
Ala His Asp Lys Arg Gly Arg Tyr Gly Thr Leu Phe Thr Met Asp Arg

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	485	490	495
5	Val Leu Thr Pro Pro Met Gly Thr Val Met Asp Val Leu Lys Gly Asp		
	500	505	510
10	Asn Arg Phe Ser Met Leu Val Ala Ala Ile Gln Ser Ala Gly Leu Thr		
	515	520	525
	Glu Thr Leu Asn Arg Glu Gly Val Tyr Thr Val Phe Ala Pro Thr Asn		
	530	535	540
15	Glu Ala Phe Arg Ala Leu Pro Pro Arg Glu Arg Ser Arg Leu Leu Gly		
	545	550	555
20	Asp Ala Lys Glu Leu Ala Asn Ile Leu Lys Tyr His Ile Gly Asp Glu		
	565	570	575
	Ile Leu Val Ser Gly Gly Ile Gly Ala Leu Val Arg Leu Lys Ser Leu		
25	580	585	590
	Gln Gly Asp Lys Leu Glu Val Ser Leu Lys Asn Asn Val Val Ser Val		
	595	600	605
30	Asn Lys Glu Pro Val Ala Glu Pro Asp Ile Met Ala Thr Asn Gly Val		
	610	615	620
35	Val His Val Ile Thr Asn Val Leu Gln Pro Pro Ala Asn Arg Pro Gln		
	625	630	635
	Glu Arg Gly Asp Glu Leu Ala Asp Ser Ala Leu Glu Ile Phe Lys Gln		
40	645	650	655
	Ala Ser Ala Phe Ser Arg Ala Ser Gln Arg Ser Val Arg Leu Ala Pro		
45	660	665	670
	Val Tyr Gln Lys Leu Leu Glu Arg Met Lys His		
	675	680	
50			
55	<210> 94		
	<211> 2355		

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<212> PRT

<213> Homo sapiens

5

<400> 94

10 Met Leu Arg Gly Pro Gly Pro Gly Leu Leu Leu Leu Ala Val Gln Cys  
1 5 10 15  
Leu Gly Thr Ala Val Pro Ser Thr Gly Ala Ser Lys Ser Lys Arg Gln  
15 20 25 30  
Ala Gln Gln Met Val Gln Pro Gln Ser Pro Val Ala Val Ser Gln Ser  
20 35 40 45  
Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr Gln Ile Asn Gln Gln  
50 55 60  
25 Trp Glu Arg Thr Tyr Leu Gly Asn Ala Leu Val Cys Thr Cys Tyr Gly  
65 70 75 80  
Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro Glu Ala Glu Glu Thr  
30 85 90 95  
Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg Val Gly Asp Thr Tyr  
35 100 105 110  
Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys Thr Cys Ile Gly Ala  
115 120 125  
40 Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn Arg Cys His Glu Gly  
130 135 140  
Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg Arg Pro His Glu Thr  
45 145 150 155 160  
Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly Asn Gly Lys Gly Glu  
50 165 170 175  
Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe Asp His Ala Ala Gly  
180 185 190  
55 Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys Pro Tyr Gln Gly Trp

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	195	200	205
	Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly Ser Gly Arg Ile Thr		
5	210	215	220
	Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp Thr Arg Thr Ser Tyr		
10	225	230	235
	Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn Arg Gly Asn Leu Leu		
	245	250	255
15	Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu Trp Lys Cys Glu Arg		
	260	265	270
20	His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser Gly Pro Phe Thr Asp		
	275	280	285
	Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His Pro Gln Pro Pro Pro		
25	290	295	300
	Tyr Gly His Cys Val Thr Asp Ser Gly Val Val Tyr Ser Val Gly Met		
30	305	310	315
	Gln Trp Leu Lys Thr Gln Gly Asn Lys Gln Met Leu Cys Thr Cys Leu		
	325	330	335
35	Gly Asn Gly Val Ser Cys Gln Glu Thr Ala Val Thr Gln Thr Tyr Gly		
	340	345	350
	Gly Asn Ser Asn Gly Glu Pro Cys Val Leu Pro Phe Thr Tyr Asn Gly		
40	355	360	365
	Arg Thr Phe Tyr Ser Cys Thr Thr Glu Gly Arg Gln Asp Gly His Leu		
45	370	375	380
	Trp Cys Ser Thr Thr Ser Asn Tyr Glu Gln Asp Gln Lys Tyr Ser Phe		
	385	390	395
50	Cys Thr Asp His Thr Val Leu Val Gln Thr Arg Gly Gly Asn Ser Asn		
	405	410	415
	Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn Asn His Asn Tyr Thr		
55	420	425	430

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	Asp	Cys	Thr	Ser	Glu	Gly	Arg	Arg	Asp	Asn	Met	Lys	Trp	Cys	Gly	Thr
						435				440					445	
5	Thr	Gln	Asn	Tyr	Asp	Ala	Asp	Gln	Lys	Phe	Gly	Phe	Cys	Pro	Met	Ala
						450				455					460	
10	Ala	His	Glu	Glu	Ile	Cys	Thr	Thr	Asn	Glu	Gly	Val	Met	Tyr	Arg	Ile
						465				470					475	
																480
	Gly	Asp	Gln	Trp	Asp	Lys	Gln	His	Asp	Met	Gly	His	Met	Met	Arg	Cys
15							485				490					495
	Thr	Cys	Val	Gly	Asn	Gly	Arg	Gly	Glu	Trp	Thr	Cys	Ile	Ala	Tyr	Ser
							500				505				510	
20	Gln	Leu	Arg	Asp	Gln	Cys	Ile	Val	Asp	Asp	Ile	Thr	Tyr	Asn	Val	Asn
						515					520				525	
25	Asp	Thr	Phe	His	Lys	Arg	His	Glu	Glu	Gly	His	Met	Leu	Asn	Cys	Thr
						530					535				540	
	Cys	Phe	Gly	Gln	Gly	Arg	Gly	Arg	Trp	Lys	Cys	Asp	Pro	Val	Asp	Gln
30						545					550				555	
																560
	Cys	Gln	Asp	Ser	Glu	Thr	Gly	Thr	Phe	Tyr	Gln	Ile	Gly	Asp	Ser	Trp
35							565				570				575	
	Glu	Lys	Tyr	Val	His	Gly	Val	Arg	Tyr	Gln	Cys	Tyr	Cys	Tyr	Gly	Arg
						580					585				590	
40	Gly	Ile	Gly	Glu	Trp	His	Cys	Gln	Pro	Leu	Gln	Thr	Tyr	Pro	Ser	Ser
						595					600				605	
45	Ser	Gly	Pro	Val	Glu	Val	Phe	Ile	Thr	Glu	Thr	Pro	Ser	Gln	Pro	Asn
						610					615				620	
	Ser	His	Pro	Ile	Gln	Trp	Asn	Ala	Pro	Gln	Pro	Ser	His	Ile	Ser	Lys
50						625					630				635	
																640
	Tyr	Ile	Leu	Arg	Trp	Arg	Pro	Lys	Asn	Ser	Val	Gly	Arg	Trp	Lys	Glu
							645				650				655	
55	Ala	Thr	Ile	Pro	Gly	His	Leu	Asn	Ser	Tyr	Thr	Ile	Lys	Gly	Leu	Lys

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	660		665		670
5	Pro Gly Val Val Tyr Glu Gly Gln Leu Ile Ser Ile Gln Gln Tyr Gly				
	675		680		685
	His Gln Glu Val Thr Arg Phe Asp Phe Thr Thr Thr Ser Thr Ser Thr				
10	690		695		700
	Pro Val Thr Ser Asn Thr Val Thr Gly Glu Thr Thr Pro Phe Ser Pro				
	705		710		715
15	Leu Val Ala Thr Ser Glu Ser Val Thr Glu Ile Thr Ala Ser Ser Phe				
	725		730		735
20	Val Val Ser Trp Val Ser Ala Ser Asp Thr Val Ser Gly Phe Arg Val				
	740		745		750
	Glu Tyr Glu Leu Ser Glu Glu Gly Asp Glu Pro Gln Tyr Leu Asp Leu				
25	755		760		765
	Pro Ser Thr Ala Thr Ser Val Asn Ile Pro Asp Leu Leu Pro Gly Arg				
	770		775		780
30	Lys Tyr Ile Val Asn Val Tyr Gln Ile Ser Glu Asp Gly Glu Gln Ser				
	785		790		795
	Leu Ile Leu Ser Thr Ser Gln Thr Thr Ala Pro Asp Ala Pro Pro Asp				
35	805		810		815
	Pro Thr Val Asp Gln Val Asp Asp Thr Ser Ile Val Val Arg Trp Ser				
40	820		825		830
	Arg Pro Gln Ala Pro Ile Thr Gly Tyr Arg Ile Val Tyr Ser Pro Ser				
45	835		840		845
	Val Glu Gly Ser Ser Thr Glu Leu Asn Leu Pro Glu Thr Ala Asn Ser				
	850		855		860
50	Val Thr Leu Ser Asp Leu Gln Pro Gly Val Gln Tyr Asn Ile Thr Ile				
	865		870		875
	Tyr Ala Val Glu Glu Asn Gln Glu Ser Thr Pro Val Val Ile Gln Gln				
55	885		890		895

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Glu Thr Thr Gly Thr Pro Arg Ser Asp Thr Val Pro Ser Pro Arg Asp  
 900 905 910  
 5 Leu Gln Phe Val Glu Val Thr Asp Val Lys Val Thr Ile Met Trp Thr  
 915 920 925  
 10 Pro Pro Glu Ser Ala Val Thr Gly Tyr Arg Val Asp Val Ile Pro Val  
 930 935 940  
 Asn Leu Pro Gly Glu His Gly Gln Arg Leu Pro Ile Ser Arg Asn Thr  
 15 945 950 955 960  
 Phe Ala Glu Val Thr Gly Leu Ser Pro Gly Val Thr Tyr Tyr Phe Lys  
 965 970 975  
 20 Val Phe Ala Val Ser His Gly Arg Glu Ser Lys Pro Leu Thr Ala Gln  
 980 985 990  
 25 Gln Thr Thr Lys Leu Asp Ala Pro Thr Asn Leu Gln Phe Val Asn Glu  
 995 1000 1005  
 Thr Asp Ser Thr Val Leu Val Arg Trp Thr Pro Pro Arg Ala Gln Ile  
 30 1010 1015 1020  
 Thr Gly Tyr Arg Leu Thr Val Gly Leu Thr Arg Arg Gly Gln Pro Arg  
 35 1025 1030 1035 1040  
 Gln Tyr Asn Val Gly Pro Ser Val Ser Lys Tyr Pro Leu Arg Asn Leu  
 1045 1050 1055  
 40 Gln Pro Ala Ser Glu Tyr Thr Val Ser Leu Val Ala Ile Lys Gly Asn  
 1060 1065 1070  
 45 Gln Glu Ser Pro Lys Ala Thr Gly Val Phe Thr Thr Leu Gln Pro Gly  
 1075 1080 1085  
 Ser Ser Ile Pro Pro Tyr Asn Thr Glu Val Thr Glu Thr Thr Ile Val  
 50 1090 1095 1100  
 Ile Thr Trp Thr Pro Ala Pro Arg Ile Gly Phe Lys Leu Gly Val Arg  
 1105 1110 1115 1120  
 55 Pro Ser Gln Gly Gly Glu Ala Pro Arg Glu Val Thr Ser Asp Ser Gly

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	1125	1130	1135
	Ser Ile Val Val Ser Gly Leu Thr Pro Gly Val Glu Tyr Val Tyr Thr		
5	1140	1145	1150
	Ile Gln Val Leu Arg Asp Gly Gln Glu Arg Asp Ala Pro Ile Val Asn		
10	1155	1160	1165
	Lys Val Val Thr Pro Leu Ser Pro Pro Thr Asn Leu His Leu Glu Ala		
	1170	1175	1180
15	Asn Pro Asp Thr Gly Val Leu Thr Val Ser Trp Glu Arg Ser Thr Thr		
	1185	1190	1195
	1200		
20	Pro Asp Ile Thr Gly Tyr Arg Ile Thr Thr Thr Pro Thr Asn Gly Gln		
	1205	1210	1215
	Gln Gly Asn Ser Leu Glu Glu Val Val His Ala Asp Gln Ser Ser Cys		
25	1220	1225	1230
	Thr Phe Asp Asn Leu Ser Pro Gly Leu Glu Tyr Asn Val Ser Val Tyr		
	1235	1240	1245
30	Thr Val Lys Asp Asp Lys Glu Ser Val Pro Ile Ser Asp Thr Ile Ile		
	1250	1255	1260
35	Pro Ala Val Pro Pro Pro Thr Asp Leu Arg Phe Thr Asn Ile Gly Pro		
	1265	1270	1275
	1280		
	Asp Thr Met Arg Val Thr Trp Ala Pro Pro Pro Ser Ile Asp Leu Thr		
40	1285	1290	1295
	Asn Phe Leu Val Arg Tyr Ser Pro Val Lys Asn Glu Glu Asp Val Ala		
45	1300	1305	1310
	Glu Leu Ser Ile Ser Pro Ser Asp Asn Ala Val Val Leu Thr Asn Leu		
	1315	1320	1325
50	Leu Pro Gly Thr Glu Tyr Val Val Ser Val Ser Ser Val Tyr Glu Gln		
	1330	1335	1340
55	His Glu Ser Thr Pro Leu Arg Gly Arg Gln Lys Thr Gly Leu Asp Ser		
	1345	1350	1355
	1360		



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Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn Ser Phe Thr Val  
1365 1370 1375  
5 His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr Arg Ile Arg His  
1380 1385 1390  
10 His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp Arg Val Pro His  
1395 1400 1405  
Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro Gly Thr Glu Tyr  
15 1410 1415 1420  
Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu Ser Pro Leu Leu  
1425 1430 1435 1440  
20 Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg Asp Leu Glu Val  
1445 1450 1455  
25 Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala  
1460 1465 1470  
Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn  
30 1475 1480 1485  
Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys Ser Thr Ala Thr  
35 1490 1495 1500  
Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala  
1505 1510 1515 1520  
40 Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys Pro Ile Ser Ile  
1525 1530 1535  
45 Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln Met Gln Val Thr Asp  
1540 1545 1550  
Val Gln Asp Asn Ser Ile Ser Val Lys Trp Leu Pro Ser Ser Ser Pro  
50 1555 1560 1565  
Val Thr Gly Tyr Arg Val Thr Thr Thr Pro Lys Asn Gly Pro Gly Pro  
1570 1575 1580  
55 Thr Lys Thr Lys Thr Ala Gly Pro Asp Gln Thr Glu Met Thr Ile Glu

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	1585	1590	1595	1600
	Gly	Leu	Gln	Pro Thr Val Glu Tyr Val Val Ser Val Tyr Ala Gln Asn
5		1605	1610	1615
	Pro	Ser Gly Glu Ser Gln Pro Leu Val Gln Thr Ala Val Thr Asn Ile		
10		1620	1625	1630
	Asp	Arg Pro Lys Gly Leu Ala Phe Thr Asp Val Asp Val Asp Ser Ile		
	1635	1640	1645	
15	Lys	Ile Ala Trp Glu Ser Pro Gln Gly Gln Val Ser Arg Tyr Arg Val		
	1650	1655	1660	
20	Thr	Tyr Ser Ser Pro Glu Asp Gly Ile His Glu Leu Phe Pro Ala Pro		
	1665	1670	1675	1680
	Asp	Gly Glu Glu Asp Thr Ala Glu Leu Gln Gly Leu Arg Pro Gly Ser		
25		1685	1690	1695
	Glu	Tyr Thr Val Ser Val Val Ala Leu His Asp Asp Met Glu Ser Gln		
	1700	1705	1710	
30	Pro	Leu Ile Gly Thr Gln Ser Thr Ala Ile Pro Ala Pro Thr Asp Leu		
	1715	1720	1725	
35	Lys	Phe Thr Gln Val Thr Pro Thr Ser Leu Ser Ala Gln Trp Thr Pro		
	1730	1735	1740	
	Pro	Asn Val Gln Leu Thr Gly Tyr Arg Val Arg Val Thr Pro Lys Glu		
40	1745	1750	1755	1760
	Lys	Thr Gly Pro Met Lys Glu Ile Asn Leu Ala Pro Asp Ser Ser Ser		
45		1765	1770	1775
	Val	Val Val Ser Gly Leu Met Val Ala Thr Lys Tyr Glu Val Ser Val		
	1780	1785	1790	
50	Tyr	Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro Ala Gln Gly Val Val		
	1795	1800	1805	
55	Thr	Thr Leu Glu Asn Val Ser Pro Pro Arg Arg Ala Arg Val Thr Asp		
	1810	1815	1820	

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Ala Thr Glu Thr Thr Ile Thr Ile Ser Trp Arg Thr Lys Thr Glu Thr  
1825 1830 1835 1840  
5 Ile Thr Gly Phe Gln Val Asp Ala Val Pro Ala Asn Gly Gln Thr Pro  
1845 1850 1855  
10 Ile Gln Arg Thr Ile Lys Pro Asp Val Arg Ser Tyr Thr Ile Thr Gly  
1860 1865 1870  
Leu Gln Pro Gly Thr Asp Tyr Lys Ile Tyr Leu Tyr Thr Leu Asn Asp  
15 1875 1880 1885  
Asn Ala Arg Ser Ser Pro Val Val Ile Asp Ala Ser Thr Ala Ile Asp  
20 1890 1895 1900  
Ala Pro Ser Asn Leu Arg Phe Leu Ala Thr Thr Pro Asn Ser Leu Leu  
1905 1910 1915 1920  
25 Val Ser Trp Gln Pro Pro Arg Ala Arg Ile Thr Gly Tyr Ile Ile Lys  
1925 1930 1935  
Tyr Glu Lys Pro Gly Ser Pro Pro Arg Glu Val Val Pro Arg Pro Arg  
30 1940 1945 1950  
Pro Gly Val Thr Glu Ala Thr Ile Thr Gly Leu Glu Pro Gly Thr Glu  
35 1955 1960 1965  
Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn Gln Lys Ser Glu Pro  
1970 1975 1980  
40 Leu Ile Gly Arg Lys Lys Thr Asp Glu Leu Pro Gln Leu Val Thr Leu  
1985 1990 1995 2000  
45 Pro His Pro Asn Leu His Gly Pro Glu Ile Leu Asp Val Pro Ser Thr  
2005 2010 2015  
Val Gln Lys Thr Pro Phe Val Thr His Pro Gly Tyr Asp Thr Gly Asn  
50 2020 2025 2030  
Gly Ile Gln Leu Pro Gly Thr Ser Gly Gln Gln Pro Ser Val Gly Gln  
55 2035 2040 2045  
Gln Met Ile Phe Glu Glu His Gly Phe Arg Arg Thr Thr Pro Pro Thr

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	2050	2055	2060
	Thr Ala Thr Pro Ile Arg His Arg Pro Arg Pro Tyr Pro Pro Asn Val		
5	2065	2070	2075 2080
	Gly Gln Glu Ala Leu Ser Gln Thr Thr Ile Ser Trp Ala Pro Phe Gln		
10	2085	2090	2095
	Asp Thr Ser Glu Tyr Ile Ile Ser Cys His Pro Val Gly Thr Asp Glu		
	2100	2105	2110
15	Glu Pro Leu Gln Phe Arg Val Pro Gly Thr Ser Thr Ser Ala Thr Leu		
	2115	2120	2125
20	Thr Gly Leu Thr Arg Gly Ala Thr Tyr Asn Ile Ile Val Glu Ala Leu		
	2130	2135	2140
	Lys Asp Gln Gln Arg His Lys Val Arg Glu Glu Val Val Thr Val Gly		
25	2145	2150	2155 2160
	Asn Ser Val Asn Glu Gly Leu Asn Gln Pro Thr Asp Asp Ser Cys Phe		
	2165	2170	2175
30	Asp Pro Tyr Thr Val Ser His Tyr Ala Val Gly Asp Glu Trp Glu Arg		
	2180	2185	2190
35	Met Ser Glu Ser Gly Phe Lys Leu Leu Cys Gln Cys Leu Gly Phe Gly		
	2195	2200	2205
	Ser Gly His Phe Arg Cys Asp Ser Ser Arg Trp Cys His Asp Asn Gly		
40	2210	2215	2220
	Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp Arg Gln Gly Glu Asn Gly		
45	2225	2230	2235 2240
	Gln Met Met Ser Cys Thr Cys Leu Gly Asn Gly Lys Gly Glu Phe Lys		
	2245	2250	2255
50	Cys Asp Pro His Glu Ala Thr Cys Tyr Asp Asp Gly Lys Thr Tyr His		
	2260	2265	2270
55	Val Gly Glu Gln Trp Gln Lys Glu Tyr Leu Gly Ala Ile Cys Ser Cys		
	2275	2280	2285

Thr Cys Phe Gly Gly Gln Arg Gly Trp Arg Cys Asp Asn Cys Arg Arg  
 2290 2295 2300  
 5 Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr Gly Gln Ser Tyr Asn  
 2305 2310 2315 2320  
 10 Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn Thr Asn Val Asn Cys  
 2325 2330 2335  
 Pro Ile Glu Cys Phe Met Pro Leu Asp Val Gln Ala Asp Arg Glu Asp  
 15 2340 2345 2350  
 Ser Arg Glu  
 20 2355  
 25 <210> 95  
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 30 <213> Homo sapiens  
 35 <400> 95  
 Met Leu Ser Phe Val Asp Thr Arg Thr Leu Leu Leu Leu Ala Val Thr  
 1 5 10 15  
 40 Leu Cys Leu Ala Thr Cys Gln Ser Leu Gln Glu Glu Thr Val Arg Lys  
 20 25 30  
 45 Gly Pro Ala Gly Asp Arg Gly Pro Arg Gly Glu Arg Gly Pro Pro Gly  
 35 40 45  
 Pro Pro Gly Arg Asp Gly Glu Asp Gly Pro Thr Gly Pro Pro Gly Pro  
 50 50 55 60  
 Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala Ala Gln  
 55 65 70 75 80  
 Tyr Asp Gly Lys Gly Val Gly Leu Gly Pro Gly Pro Met Gly Leu Met

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	85	90	95
5	Gly Pro Arg Gly Pro Pro Gly Ala Ala Gly Ala Pro Gly Pro Gln Gly		
	100	105	110
10	Phe Gln Gly Pro Ala Gly Glu Pro Gly Glu Pro Gly Gln Thr Gly Pro		
	115	120	125
15	Ala Gly Ala Arg Gly Pro Ala Gly Pro Pro Gly Lys Ala Gly Glu Asp		
	130	135	140
20	Gly His Pro Gly Lys Pro Gly Arg Pro Gly Glu Arg Gly Val Val Gly		
	145	150	155
25	Pro Gln Gly Ala Arg Gly Phe Pro Gly Thr Pro Gly Leu Pro Gly Phe		
	165	170	175
30	Lys Gly Ile Arg Gly His Asn Gly Leu Asp Gly Leu Lys Gly Gln Pro		
	180	185	190
35	Gly Ala Pro Gly Val Lys Gly Glu Pro Gly Ala Pro Gly Glu Asn Gly		
	195	200	205
40	Thr Pro Gly Gln Thr Gly Ala Arg Gly Leu Pro Gly Glu Arg Gly Arg		
	210	215	220
45	Val Gly Ala Pro Gly Pro Ala Gly Ala Arg Gly Ser Asp Gly Ser Val		
	225	230	235
50	Gly Pro Val Gly Pro Ala Gly Pro Ile Gly Ser Ala Gly Pro Pro Gly		
	245	250	255
55	Phe Pro Gly Ala Pro Gly Pro Lys Gly Glu Ile Gly Ala Val Gly Asn		
	260	265	270
	Ala Gly Pro Ala Gly Pro Ala Gly Pro Arg Gly Glu Val Gly Leu Pro		
	275	280	285
	Gly Leu Ser Gly Pro Val Gly Pro Pro Gly Asn Pro Gly Ala Asn Gly		
	290	295	300
	Leu Thr Gly Ala Lys Gly Ala Ala Gly Leu Pro Gly Val Ala Gly Ala		
	305	310	315
			320

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Pro Gly Leu Pro Gly Pro Arg Gly Ile Pro Gly Pro Val Gly Ala Ala  
325 330 335  
5 Gly Ala Thr Gly Ala Arg Gly Leu Val Gly Glu Pro Gly Pro Ala Gly  
340 345 350  
10 Ser Lys Gly Glu Ser Gly Asn Lys Gly Glu Pro Gly Ser Ala Gly Pro  
355 360 365  
Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu Gly Lys Arg Gly Pro Asn  
15 370 375 380  
Gly Glu Ala Gly Ser Ala Gly Pro Pro Gly Pro Pro Gly Leu Arg Gly  
20 385 390 395 400  
Ser Pro Gly Ser Arg Gly Leu Pro Gly Ala Asp Gly Arg Ala Gly Val  
405 410 415  
25 Met Gly Pro Pro Gly Ser Arg Gly Ala Ser Gly Pro Ala Gly Val Arg  
420 425 430  
Gly Pro Asn Gly Asp Ala Gly Arg Pro Gly Glu Pro Gly Leu Met Gly  
30 435 440 445  
Pro Arg Gly Leu Pro Gly Ser Pro Gly Asn Ile Gly Pro Ala Gly Lys  
35 450 455 460  
Glu Gly Pro Val Gly Leu Pro Gly Ile Asp Gly Arg Pro Gly Pro Ile  
465 470 475 480  
40 Gly Pro Ala Gly Ala Arg Gly Glu Pro Gly Asn Ile Gly Phe Pro Gly  
485 490 495  
45 Pro Lys Gly Pro Thr Gly Asp Pro Gly Lys Asn Gly Asp Lys Gly His  
500 505 510  
Ala Gly Leu Ala Gly Ala Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn  
50 515 520 525  
Gly Ala Gln Gly Pro Pro Gly Pro Gln Gly Val Gln Gly Gly Lys Gly  
530 535 540  
55 Glu Gln Gly Pro Ala Gly Pro Pro Gly Phe Gln Gly Leu Pro Gly Pro

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	545	550	555	560
	Ser Gly Pro Ala Gly Glu Val Gly Lys Pro Gly Glu Arg Gly Leu His			
5		565	570	575
	Gly Glu Phe Gly Leu Pro Gly Pro Ala Gly Pro Arg Gly Glu Arg Gly			
10		580	585	590
	Pro Pro Gly Glu Ser Gly Ala Ala Gly Pro Thr Gly Pro Ile Gly Ser			
	595	600	605	
15	Arg Gly Pro Ser Gly Pro Pro Gly Pro Asp Gly Asn Lys Gly Glu Pro			
	610	615	620	
20	Gly Val Val Gly Ala Val Gly Thr Ala Gly Pro Ser Gly Pro Ser Gly			
	625	630	635	640
	Leu Pro Gly Glu Arg Gly Ala Ala Gly Ile Pro Gly Gly Lys Gly Glu			
25		645	650	655
	Lys Gly Glu Pro Gly Leu Arg Gly Glu Ile Gly Asn Pro Gly Arg Asp			
	660	665	670	
30	Gly Ala Arg Gly Ala His Gly Ala Val Gly Ala Pro Gly Pro Ala Gly			
	675	680	685	
35	Ala Thr Gly Asp Arg Gly Glu Ala Gly Ala Ala Gly Pro Ala Gly Pro			
	690	695	700	
	Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg Gly Glu Val Gly Pro Ala			
40	705	710	715	720
	Gly Pro Asn Gly Phe Ala Gly Pro Ala Gly Ala Ala Gly Gln Pro Gly			
45		725	730	735
	Ala Lys Gly Glu Arg Gly Ala Lys Gly Pro Lys Gly Glu Asn Gly Val			
	740	745	750	
50	Val Gly Pro Thr Gly Pro Val Gly Ala Ala Gly Pro Ala Gly Pro Asn			
	755	760	765	
55	Gly Pro Pro Gly Pro Ala Gly Ser Arg Gly Asp Gly Gly Pro Pro Gly			
	770	775	780	



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Met Thr Gly Phe Pro Gly Ala Ala Gly Arg Thr Gly Pro Pro Gly Pro  
785 790 795 800  
5 Ser Gly Ile Ser Gly Pro Pro Gly Pro Pro Gly Pro Ala Gly Lys Glu  
805 810 815  
10 Gly Leu Arg Gly Pro Arg Gly Asp Gln Gly Pro Val Gly Arg Thr Gly  
820 825 830  
Glu Val Gly Ala Val Gly Pro Pro Gly Phe Ala Gly Glu Lys Gly Pro  
15 835 840 845  
Ser Gly Glu Ala Gly Thr Ala Gly Pro Pro Gly Thr Pro Gly Pro Gln  
20 850 855 860  
Gly Leu Leu Gly Ala Pro Gly Ile Leu Gly Leu Pro Gly Ser Arg Gly  
865 870 875 880  
25 Glu Arg Gly Leu Pro Gly Val Ala Gly Ala Val Gly Glu Pro Gly Pro  
885 890 895  
30 Leu Gly Ile Ala Gly Pro Pro Gly Ala Arg Gly Pro Pro Gly Ala Val  
900 905 910  
Gly Ser Pro Gly Val Asn Gly Ala Pro Gly Glu Ala Gly Arg Asp Gly  
35 915 920 925  
Asn Pro Gly Asn Asp Gly Pro Pro Gly Arg Asp Gly Gln Pro Gly His  
930 935 940  
40 Lys Gly Glu Arg Gly Tyr Pro Gly Asn Ile Gly Pro Val Gly Ala Ala  
945 950 955 960  
45 Gly Ala Pro Gly Pro His Gly Pro Val Gly Pro Ala Gly Lys His Gly  
965 970 975  
Asn Arg Gly Glu Thr Gly Pro Ser Gly Pro Val Gly Pro Ala Gly Ala  
50 980 985 990  
Val Gly Pro Arg Gly Pro Ser Gly Pro Gln Gly Ile Arg Gly Asp Lys  
995 1000 1005  
55 Gly Glu Pro Gly Glu Lys Gly Pro Arg Gly Leu Pro Gly Leu Lys Gly

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	1010	1015	1020
	His Asn Gly Leu Gln Gly Leu Pro Gly Ile Ala Gly His His Gly Asp		
5	1025	1030	1035 1040
	Gln Gly Ala Pro Gly Ser Val Gly Pro Ala Gly Pro Arg Gly Pro Ala		
10	1045	1050	1055
	Gly Pro Ser Gly Pro Ala Gly Lys Asp Gly Arg Thr Gly His Pro Gly		
	1060	1065	1070
15	Thr Val Gly Pro Ala Gly Ile Arg Gly Pro Gln Gly His Gln Gly Pro		
	1075	1080	1085
20	Ala Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Val Ser		
	1090	1095	1100
	Gly Gly Gly Tyr Asp Phe Gly Tyr Asp Gly Asp Phe Tyr Arg Ala Asp		
25	1105	1110	1115 1120
	Gln Pro Arg Ser Ala Pro Ser Leu Arg Pro Lys Asp Tyr Glu Val Asp		
	1125	1130	1135
30	Ala Thr Leu Lys Ser Leu Asn Asn Gln Ile Glu Thr Leu Leu Thr Pro		
	1140	1145	1150
35	Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Arg Leu		
	1155	1160	1165
	Ser His Pro Glu Trp Ser Ser Gly Tyr Tyr Trp Ile Asp Pro Asn Gln		
40	1170	1175	1180
	Gly Cys Thr Met Asp Ala Ile Lys Val Tyr Cys Asp Phe Ser Thr Gly		
45	1185	1190	1195 1200
	Glu Thr Cys Ile Arg Ala Gln Pro Glu Asn Ile Pro Ala Lys Asn Trp		
	1205	1210	1215
50	Tyr Arg Ser Ser Lys Asp Lys Lys His Val Trp Leu Gly Glu Thr Ile		
	1220	1225	1230
	Asn Ala Gly Ser Gln Phe Glu Tyr Asn Val Glu Gly Val Thr Ser Lys		
55	1235	1240	1245

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Glu Met Ala Thr Gln Leu Ala Phe Met Arg Leu Leu Ala Asn Tyr Ala  
 1250 1255 1260  
 5 Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile Ala Tyr Met Asp  
 1265 1270 1275 1280  
 10 Glu Glu Thr Gly Asn Leu Lys Lys Ala Val Ile Leu Gln Gly Ser Asn  
 1285 1290 1295  
 Asp Val Glu Leu Val Ala Glu Gly Asn Ser Arg Phe Thr Tyr Thr Val  
 15 1300 1305 1310  
 Leu Val Asp Gly Cys Ser Lys Lys Thr Asn Glu Trp Gly Lys Thr Ile  
 20 1315 1320 1325  
 Ile Glu Tyr Lys Thr Asn Lys Pro Ser Arg Leu Pro Phe Leu Asp Ile  
 1330 1335 1340  
 25 Ala Pro Leu Asp Ile Gly Gly Ala Asp His Glu Phe Phe Val Asp Ile  
 1345 1350 1355 1360  
 30 Gly Pro Val Cys Phe Lys  
 1365  
 35  
 <210> 96  
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 40 <212> PRT  
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 45  
 <400> 96  
 Met Ala Lys Ile Ser Ser Pro Thr Glu Thr Glu Arg Cys Ile Glu Ser  
 50 1 5 10 15  
 Leu Ile Ala Val Phe Gln Lys Tyr Ala Gly Lys Asp Gly Tyr Asn Tyr  
 55 20 25 30  
 Thr Leu Ser Lys Thr Glu Phe Leu Ser Phe Met Asn Thr Glu Leu Ala

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35 40 45  
 5 Ala Phe Thr Lys Asn Gln Lys Asp Pro Gly Val Leu Asp Arg Met Met  
 50 55 60  
 Lys Lys Leu Asp Thr Asn Ser Asp Gly Gln Leu Asp Phe Ser Glu Phe  
 10 65 70 75 80  
 Leu Asn Leu Ile Gly Gly Leu Ala Met Ala Cys His Asp Ser Phe Leu  
 85 90 95  
 15 Lys Ala Val Pro Ser Gln Lys Arg Thr  
 100 105  
 20  
 <210> 97  
 25 <211> 283  
 <212> PRT  
 30 <213> Homo sapiens  
 <400> 97  
 35 Met Val Asn Tyr Ala Trp Ala Gly Arg Ser Gln Arg Lys Leu Trp Trp  
 1 5 10 15  
 Arg Ser Val Ala Val Leu Thr Cys Lys Ser Val Val Arg Pro Gly Tyr  
 40 20 25 30  
 Arg Gly Gly Leu Gln Ala Arg Arg Ser Thr Leu Leu Lys Thr Cys Ala  
 45 35 40 45  
 Arg Ala Arg Ala Thr Ala Pro Gly Ala Met Lys Met Val Ala Pro Trp  
 50 55 60  
 50 Thr Arg Phe Tyr Ser Asn Ser Cys Cys Leu Cys Cys His Val Arg Thr  
 65 70 75 80  
 Gly Thr Ile Leu Leu Gly Val Trp Tyr Leu Ile Ile Asn Ala Val Val  
 55 85 90 95

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Leu Leu Ile Leu Leu Ser Ala Leu Ala Asp Pro Asp Gln Tyr Asn Phe  
 100 105 110  
 5 Ser Ser Ser Glu Leu Gly Gly Asp Phe Glu Phe Met Asp Asp Ala Asn  
 115 120 125  
 10 Met Cys Ile Ala Ile Ala Ile Ser Leu Leu Met Ile Leu Ile Cys Ala  
 130 135 140  
 Met Ala Thr Tyr Gly Ala Tyr Lys Gln Arg Ala Ala Trp Ile Ile Pro  
 15 145 150 155 160  
 Phe Phe Cys Tyr Gln Ile Phe Asp Phe Ala Leu Asn Met Leu Val Ala  
 165 170 175  
 20 Ile Thr Val Leu Ile Tyr Pro Asn Ser Ile Gln Glu Tyr Ile Arg Gln  
 180 185 190  
 25 Leu Pro Pro Asn Phe Pro Tyr Arg Asp Asp Val Met Ser Val Asn Pro  
 195 200 205  
 Thr Cys Leu Val Leu Ile Ile Leu Leu Phe Ile Ser Ile Ile Leu Thr  
 30 210 215 220  
 Phe Lys Gly Tyr Leu Ile Ser Cys Val Trp Asn Cys Tyr Arg Tyr Ile  
 35 225 230 235 240  
 Asn Gly Arg Asn Ser Ser Asp Val Leu Val Tyr Val Thr Ser Asn Asp  
 245 250 255  
 40 Thr Thr Val Leu Leu Pro Pro Tyr Asp Asp Ala Thr Val Asn Gly Ala  
 260 265 270  
 45 Ala Lys Glu Pro Pro Pro Pro Tyr Val Ser Ala  
 275 280  
 50  
 <210> 98  
 <211> 712  
 55 <212> PRT

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<213> Homo sapiens

5

<400> 98

Met Ala Gly Gly Pro Gly Pro Gly Glu Pro Ala Ala Pro Gly Ala Gln

10

1 5 10 15

His Phe Leu Tyr Glu Val Pro Pro Trp Val Met Cys Arg Phe Tyr Lys

20 25 30

15

Val Met Asp Ala Leu Glu Pro Ala Asp Trp Cys Gln Phe Ala Ala Leu

35 40 45

20

Ile Val Arg Asp Gln Thr Glu Leu Arg Leu Cys Glu Arg Ser Gly Gln

50 55 60

Arg Thr Ala Ser Val Leu Trp Pro Trp Ile Asn Arg Asn Ala Arg Val

25

65 70 75 80

Ala Asp Leu Val His Ile Leu Thr His Leu Gln Leu Leu Arg Ala Arg

85 90 95

30

Asp Ile Ile Thr Ala Trp His Pro Pro Ala Pro Leu Pro Ser Pro Gly

100 105 110

35

Thr Thr Ala Pro Arg Pro Ser Ser Ile Pro Ala Pro Ala Glu Ala Glu

115 120 125

Ala Trp Ser Pro Arg Lys Leu Pro Ser Ser Ala Ser Thr Phe Leu Ser

40

130 135 140

Pro Ala Phe Pro Gly Ser Gln Thr His Ser Gly Pro Glu Leu Gly Leu

45

145 150 155 160

Val Pro Ser Pro Ala Ser Leu Trp Pro Pro Pro Pro Ser Pro Ala Pro

165 170 175

50

Ser Ser Thr Lys Pro Gly Pro Glu Ser Ser Val Ser Leu Leu Gln Gly

180 185 190

55

Ala Arg Pro Ser Pro Phe Cys Trp Pro Leu Cys Glu Ile Ser Arg Gly

195 200 205

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Thr His Asn Phe Ser Glu Glu Leu Lys Ile Gly Glu Gly Gly Phe Gly  
 210 215 220  
 5 Cys Val Tyr Arg Ala Val Met Arg Asn Thr Val Tyr Ala Val Lys Arg  
 225 230 235 240  
 10 Leu Lys Glu Asn Ala Asp Leu Glu Trp Thr Ala Val Lys Gln Ser Phe  
 245 250 255  
 Leu Thr Glu Val Glu Gln Leu Ser Arg Phe Arg His Pro Asn Ile Val  
 15 260 265 270  
 Asp Phe Ala Gly Tyr Cys Ala Gln Asn Gly Phe Tyr Cys Leu Val Tyr  
 275 280 285  
 20 Gly Phe Leu Pro Asn Gly Ser Leu Glu Asp Arg Leu His Cys Gln Thr  
 290 295 300  
 25 Gln Ala Cys Pro Pro Leu Ser Trp Pro Gln Arg Leu Asp Ile Leu Leu  
 305 310 315 320  
 Gly Thr Ala Arg Ala Ile Gln Phe Leu His Gln Asp Ser Pro Ser Leu  
 30 325 330 335  
 Ile His Gly Asp Ile Lys Ser Ser Asn Val Leu Leu Asp Glu Arg Leu  
 35 340 345 350  
 Thr Pro Lys Leu Gly Asp Phe Gly Leu Ala Arg Phe Ser Arg Phe Ala  
 355 360 365  
 40 Gly Ser Ser Pro Ser Gln Ser Ser Met Val Ala Arg Thr Gln Thr Val  
 370 375 380  
 45 Arg Gly Thr Leu Ala Tyr Leu Pro Glu Glu Tyr Ile Lys Thr Gly Arg  
 385 390 395 400  
 Leu Ala Val Asp Thr Asp Thr Phe Ser Phe Gly Val Val Val Leu Glu  
 50 405 410 415  
 Thr Leu Ala Gly Gln Arg Ala Val Lys Thr His Gly Ala Arg Thr Lys  
 420 425 430  
 55 Tyr Leu Lys Asp Leu Val Glu Glu Glu Ala Glu Glu Ala Gly Val Ala

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	435	440	445
5	Leu Arg Ser Thr Gln Ser Thr	Leu Gln Ala Gly Leu Ala Ala Asp Ala	
	450	455	460
	Trp Ala Ala Pro Ile Ala Met Gln Ile Tyr Lys Lys His Leu Asp Pro		
10	465	470	475 480
	Arg Pro Gly Pro Cys Pro Pro Glu Leu Gly Leu Gly Leu Gly Gln Leu		
	485	490	495
15	Ala Cys Cys Cys Leu His Arg Arg Ala Lys Arg Arg Pro Pro Met Thr		
	500	505	510
20	Gln Val Tyr Glu Arg Leu Glu Lys Leu Gln Ala Val Val Ala Gly Val		
	515	520	525
	Pro Gly His Leu Glu Ala Ala Ser Cys Ile Pro Pro Ser Pro Gln Glu		
25	530	535	540
	Asn Ser Tyr Val Ser Ser Thr Gly Arg Ala His Ser Gly Ala Ala Pro		
30	545	550	555 560
	Trp Gln Pro Leu Ala Ala Pro Ser Gly Ala Ser Ala Gln Ala Ala Glu		
	565	570	575
35	Gln Leu Gln Arg Gly Pro Asn Gln Pro Val Glu Ser Asp Glu Ser Leu		
	580	585	590
40	Gly Gly Leu Ser Ala Ala Leu Arg Ser Trp His Leu Thr Pro Ser Cys		
	595	600	605
	Pro Leu Asp Pro Ala Pro Leu Arg Glu Ala Gly Cys Pro Gln Gly Asp		
45	610	615	620
	Thr Ala Gly Glu Ser Ser Trp Gly Ser Gly Pro Gly Ser Arg Pro Thr		
	625	630	635 640
50	Ala Val Glu Gly Leu Ala Leu Gly Ser Ser Ala Ser Ser Ser Ser Glu		
	645	650	655
55	Pro Pro Gln Ile Ile Ile Asn Pro Ala Arg Gln Lys Met Val Gln Lys		
	660	665	670



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Leu Ala Leu Tyr Glu Asp Gly Ala Leu Asp Ser Leu Gln Leu Leu Ser  
 5                   675                   680                   685  
 Ser Ser Ser Leu Pro Gly Leu Gly Leu Glu Gln Asp Arg Gln Gly Pro  
                  690                   695                   700  
 10 Glu Glu Ser Asp Glu Phe Gln Ser  
      705                   710  
 15  
 <210> 99  
 20 <211> 132  
 <212> PRT  
 <213> Homo sapiens  
 25  
 <400> 99  
 30 Met Asn His Ile Val Gln Thr Phe Ser Pro Val Asn Ser Gly Gln Pro  
      1                   5                   10                   15  
 Pro Asn Tyr Glu Met Leu Lys Glu Glu Gln Glu Val Ala Met Leu Gly  
 35                   20                   25                   30  
 Gly Pro His Asn Pro Ala Pro Pro Thr Ser Thr Val Ile His Ile Arg  
                  35                   40                   45  
 40 Ser Glu Thr Ser Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr  
      50                   55                   60  
 45 Leu Phe Met Asn Thr Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr Ser  
      65                   70                   75                   80  
 Val Lys Ser Arg Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala Gln  
 50                   85                   90                   95  
 Ala Tyr Ala Ser Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile Leu  
                  100                   105                   110  
 55 Gly Ile Phe Met Thr Ile Leu Leu Val Ile Ile Pro Val Leu Val Val

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115 120 125  
 5 Gln Ala Gln Arg  
 130  
 10  
 <210> 100  
 15 <211> 207  
 <212> PRT  
 <213> Homo sapiens  
 20  
 <400> 100  
 25 Met Ala Pro Phe Glu Pro Leu Ala Ser Gly Ile Leu Leu Leu Leu Trp  
 1 5 10 15  
 Leu Ile Ala Pro Ser Arg Ala Cys Thr Cys Val Pro Pro His Pro Gln  
 30 20 25 30  
 Thr Ala Phe Cys Asn Ser Asp Leu Val Ile Arg Ala Lys Phe Val Gly  
 35 35 40 45  
 Thr Pro Glu Val Asn Gln Thr Thr Leu Tyr Gln Arg Tyr Glu Ile Lys  
 50 55 60  
 40 Met Thr Lys Met Tyr Lys Gly Phe Gln Ala Leu Gly Asp Ala Ala Asp  
 65 70 75 80  
 Ile Arg Phe Val Tyr Thr Pro Ala Met Glu Ser Val Cys Gly Tyr Phe  
 45 85 90 95  
 His Arg Ser His Asn Arg Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu  
 100 105 110  
 50 Gln Asp Gly Leu Leu His Ile Thr Thr Cys Ser Phe Val Ala Pro Trp  
 115 120 125  
 55 Asn Ser Leu Ser Leu Ala Gln Arg Arg Gly Phe Thr Lys Thr Tyr Thr  
 130 135 140

Val Gly Cys Glu Glu Cys Thr Val Phe Pro Cys Leu Ser Ile Pro Cys  
 5 145 150 155 160  
 Lys Leu Gln Ser Gly Thr His Cys Leu Trp Thr Asp Gln Leu Leu Gln  
 165 170 175  
 10 Gly Ser Glu Lys Gly Phe Gln Ser Arg His Leu Ala Cys Leu Pro Arg  
 180 185 190  
 15 Glu Pro Gly Leu Cys Thr Trp Gln Ser Leu Arg Ser Gln Ile Ala  
 195 200 205  
 20  
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 25 <212> PRT  
 <213> Homo sapiens  
 30  
 <400> 101  
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 35 1 5 10 15  
 Leu Leu Leu Leu Leu Pro Leu Ser Ser Ser Ser Ser Ser Asp Thr Cys  
 20 25 30  
 40 Gly Pro Cys Glu Pro Ala Ser Cys Pro Pro Leu Pro Pro Leu Gly Cys  
 35 40 45  
 45 Leu Leu Gly Glu Thr Arg Asp Ala Cys Gly Cys Cys Pro Met Cys Ala  
 50 55 60  
 Arg Gly Glu Gly Glu Pro Cys Gly Gly Gly Gly Ala Gly Arg Gly Tyr  
 50 65 70 75 80  
 Cys Ala Pro Gly Met Glu Cys Val Lys Ser Arg Lys Arg Arg Lys Gly  
 85 90 95  
 55 Lys Ala Gly Ala Ala Ala Gly Gly Pro Gly Val Ser Gly Val Cys Val

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	100	105	110
5	Cys Lys Ser Arg Tyr Pro Val Cys Gly Ser Asp Gly Thr Thr Tyr Pro		
	115	120	125
10	Ser Gly Cys Gln Leu Arg Ala Ala Ser Gln Arg Ala Glu Ser Arg Gly		
	130	135	140
	Glu Lys Ala Ile Thr Gln Val Ser Lys Gly Thr Cys Glu Gln Gly Pro		
15	145	150	155
	Ser Ile Val Thr Pro Pro Lys Asp Ile Trp Asn Val Thr Gly Ala Gln		
	165	170	175
20	Val Tyr Leu Ser Cys Glu Val Ile Gly Ile Pro Thr Pro Val Leu Ile		
	180	185	190
25	Trp Asn Lys Val Lys Arg Gly His Tyr Gly Val Gln Arg Thr Glu Leu		
	195	200	205
	Leu Pro Gly Asp Arg Asp Asn Leu Ala Ile Gln Thr Arg Gly Gly Pro		
30	210	215	220
	Glu Lys His Glu Val Thr Gly Trp Val Leu Val Ser Pro Leu Ser Lys		
	225	230	235
35	Glu Asp Ala Gly Glu Tyr Glu Cys His Ala Ser Asn Ser Gln Gly Gln		
	245	250	255
40	Ala Ser Ala Ser Ala Lys Ile Thr Val Val Asp Ala Leu His Glu Ile		
	260	265	270
	Pro Val Lys Lys Gly Glu Gly Ala Glu Leu		
45	275	280	
50	<210> 102		
	<211> 125		
	<212> PRT		
55	<213> Homo sapiens		

5 <400> 102

Met His Lys Glu Glu His Glu Val Ala Val Leu Gly Ala Pro Pro Ser

1 5 10 15

10 Thr Ile Leu Pro Arg Ser Thr Val Ile Asn Ile His Ser Glu Thr Ser

20 25 30

15 Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr Leu Phe Leu Asn

35 40 45

Trp Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr Ser Val Lys Ser Arg

20 50 55 60

Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala Gln Ala Tyr Ala Ser

65 70 75 80

25 Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile Leu Gly Ile Leu Met

85 90 95

30 Thr Ile Gly Phe Ile Leu Leu Leu Val Phe Gly Ser Val Thr Val Tyr

100 105 110

His Ile Met Leu Gln Ile Ile Gln Glu Lys Arg Gly Tyr

35 115 120 125

40 <210> 103

<211> 1466

45 <212> PRT

<213> Homo sapiens

50 <400> 103

Met Met Ser Phe Val Gln Lys Gly Ser Trp Leu Leu Leu Ala Leu Leu

1 5 10 15

55 His Pro Thr Ile Ile Leu Ala Gln Gln Glu Ala Val Glu Gly Gly Cys

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	20	25	30
5	Ser His Leu Gly Gln Ser Tyr Ala Asp Arg Asp Val Trp Lys Pro Glu		
	35	40	45
	Pro Cys Gln Ile Cys Val Cys Asp Ser Gly Ser Val Leu Cys Asp Asp		
10	50	55	60
	Ile Ile Cys Asp Asp Gln Glu Leu Asp Cys Pro Asn Pro Glu Ile Pro		
	65	70	75
15	Phe Gly Glu Cys Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro Thr		
	85	90	95
20	Arg Pro Pro Asn Gly Gln Gly Pro Gln Gly Pro Lys Gly Asp Pro Gly		
	100	105	110
	Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Ile Pro Gly Gln		
25	115	120	125
	Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro Gly Ile Cys Glu Ser Cys		
30	130	135	140
	Pro Thr Gly Pro Gln Asn Tyr Ser Pro Gln Tyr Asp Ser Tyr Asp Val		
	145	150	155
35	Lys Ser Gly Val Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala		
	165	170	175
	Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Thr Ser Gly His Pro Gly		
40	180	185	190
	Ser Pro Gly Ser Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln		
45	195	200	205
	Ala Gly Pro Ser Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro Ser		
	210	215	220
50	Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg Pro Gly		
	225	230	235
	Glu Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly Ile		
55	245	250	255

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Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly Phe Asp Gly Arg Asn  
5                   260                   265                   270  
Gly Glu Lys Gly Glu Thr Gly Ala Pro Gly Leu Lys Gly Glu Asn Gly  
                  275                   280                   285  
10 Leu Pro Gly Glu Asn Gly Ala Pro Gly Pro Met Gly Pro Arg Gly Ala  
                  290                   295                   300  
Pro Gly Glu Arg Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg  
15 305                   310                   315                   320  
Gly Asn Asp Gly Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly  
20                   325                   330                   335  
Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala Lys Gly Glu  
                  340                   345                   350  
25 Val Gly Pro Ala Gly Ser Pro Gly Ser Asn Gly Ala Pro Gly Gln Arg  
                  355                   360                   365  
Gly Glu Pro Gly Pro Gln Gly His Ala Gly Ala Gln Gly Pro Pro Gly  
30 370                   375                   380  
Pro Pro Gly Ile Asn Gly Ser Pro Gly Gly Lys Gly Glu Met Gly Pro  
35 385                   390                   395                   400  
Ala Gly Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro  
                  405                   410                   415  
40 Gly Pro Ala Gly Ala Asn Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly  
                  420                   425                   430  
45 Glu Pro Gly Lys Asn Gly Ala Lys Gly Glu Pro Gly Pro Arg Gly Glu  
                  435                   440                   445  
Arg Gly Glu Ala Gly Ile Pro Gly Val Pro Gly Ala Lys Gly Glu Asp  
50 450                   455                   460  
Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala Asn Gly Leu Pro Gly  
465                   470                   475                   480  
55 Ala Ala Gly Glu Arg Gly Ala Pro Gly Phe Arg Gly Pro Ala Gly Pro

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	485	490	495
5	Asn Gly Ile Pro Gly Glu Lys Gly Pro Ala Gly Glu Arg Gly Ala Pro		
	500	505	510
	Gly Pro Ala Gly Pro Arg Gly Ala Ala Gly Glu Pro Gly Arg Asp Gly		
10	515	520	525
	Val Pro Gly Gly Pro Gly Met Arg Gly Met Pro Gly Ser Pro Gly Gly		
	530	535	540
15	Pro Gly Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Ser		
	545	550	555
	Gly Arg Pro Gly Pro Pro Gly Pro Ser Gly Pro Arg Gly Gln Pro Gly		
20	565	570	575
	Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly Ala Pro Gly Lys		
25	580	585	590
	Asn Gly Glu Arg Gly Gly Pro Gly Gly Pro Gly Pro Gln Gly Pro Pro		
	595	600	605
30	Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr Gly		
	610	615	620
35	Pro Gly Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu		
	625	630	635
	Gln Gly Leu Pro Gly Thr Gly Gly Pro Pro Gly Glu Asn Gly Lys Pro		
40	645	650	655
	Gly Glu Pro Gly Pro Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly		
45	660	665	670
	Gly Lys Gly Asp Ala Gly Ala Pro Gly Glu Arg Gly Pro Pro Gly Leu		
	675	680	685
50	Ala Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu		
	690	695	700
	Gly Gly Lys Gly Ala Ala Gly Pro Pro Gly Pro Pro Gly Ala Ala Gly		
55	705	710	715
			720



Thr Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Gly Leu Gly Ser  
 5                               725                               730                               735  
 Pro Gly Pro Lys Gly Asp Lys Gly Glu Pro Gly Gly Pro Gly Ala Asp  
                               740                               745                               750  
 10 Gly Val Pro Gly Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly  
                               755                               760                               765  
 Pro Pro Gly Pro Ala Gly Gln Pro Gly Asp Lys Gly Glu Gly Gly Ala  
 15                               770                               775                               780  
 Pro Gly Leu Pro Gly Ile Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg  
 20                               785                               790                               795                               800  
 Gly Glu Thr Gly Pro Pro Gly Pro Ala Gly Phe Pro Gly Ala Pro Gly  
                               805                               810                               815  
 25 Gln Asn Gly Glu Pro Gly Gly Lys Gly Glu Arg Gly Ala Pro Gly Glu  
                               820                               825                               830  
 Lys Gly Glu Gly Gly Pro Pro Gly Val Ala Gly Pro Pro Gly Gly Ser  
 30                               835                               840                               845  
 Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly Val Lys Gly Glu Arg Gly  
 35                               850                               855                               860  
 Ser Pro Gly Gly Pro Gly Ala Ala Gly Phe Pro Gly Ala Arg Gly Leu  
 865                               870                               875                               880  
 40 Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Pro Ser  
                               885                               890                               895  
 Gly Ser Pro Gly Lys Asp Gly Pro Pro Gly Pro Ala Gly Asn Thr Gly  
 45                               900                               905                               910  
 Ala Pro Gly Ser Pro Gly Val Ser Gly Pro Lys Gly Asp Ala Gly Gln  
 50                               915                               920                               925  
 Pro Gly Glu Lys Gly Ser Pro Gly Ala Gln Gly Pro Pro Gly Ala Pro  
 930                               935                               940  
 55 Gly Pro Leu Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly

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	945	950	955	960
5	Pro Pro Gly Met	Pro Gly Pro Arg Gly Ser	Pro Gly Pro Gln Gly Val	
	965	970	975	
	Lys Gly Glu Ser Gly Lys	Pro Gly Ala Asn Gly Leu Ser Gly Glu Arg		
10	980	985	990	
	Gly Pro Pro Gly Pro Gln Gly Leu	Pro Gly Leu Ala Gly Thr Ala Gly		
	995	1000	1005	
15	Glu Pro Gly Arg Asp Gly Asn	Pro Gly Ser Asp Gly Leu Pro Gly Arg		
	1010	1015	1020	
20	Asp Gly Ser Pro Gly Gly Lys Gly	Asp Arg Gly Glu Asn Gly Ser Pro		
	1025	1030	1035	1040
	Gly Ala Pro Gly Ala Pro Gly His	Pro Gly Pro Pro Gly Pro Val Gly		
25	1045	1050	1055	
	Pro Ala Gly Lys Ser Gly Asp Arg	Gly Glu Ser Gly Pro Ala Gly Pro		
	1060	1065	1070	
30	Ala Gly Ala Pro Gly Pro Ala Gly	Ser Arg Gly Ala Pro Gly Pro Gln		
	1075	1080	1085	
35	Gly Pro Arg Gly Asp Lys Gly Glu Thr	Gly Glu Arg Gly Ala Ala Gly		
	1090	1095	1100	
	Ile Lys Gly His Arg Gly Phe Pro	Gly Asn Pro Gly Ala Pro Gly Ser		
40	1105	1110	1115	1120
	Pro Gly Pro Ala Gly Gln Gln Gly	Ala Ile Gly Ser Pro Gly Pro Ala		
	1125	1130	1135	
45	Gly Pro Arg Gly Pro Val Gly Pro Ser	Gly Pro Pro Gly Lys Asp Gly		
	1140	1145	1150	
50	Thr Ser Gly His Pro Gly Pro Ile Gly	Pro Pro Gly Pro Arg Gly Asn		
	1155	1160	1165	
	Arg Gly Glu Arg Gly Ser Glu Gly Ser	Pro Gly His Pro Gly Gln Pro		
55	1170	1175	1180	

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	Gly	Pro	Pro	Gly	Pro	Pro	Gly	Ala	Pro	Gly	Pro	Cys	Cys	Gly	Gly	Val
5	1185						1190					1195				1200
	Gly	Ala	Ala	Ala	Ile	Ala	Gly	Ile	Gly	Gly	Glu	Lys	Ala	Gly	Gly	Phe
						1205					1210					1215
10	Ala	Pro	Tyr	Tyr	Gly	Asp	Glu	Pro	Met	Asp	Phe	Lys	Ile	Asn	Thr	Asp
						1220					1225					1230
	Glu	Ile	Met	Thr	Ser	Leu	Lys	Ser	Val	Asn	Gly	Gln	Ile	Glu	Ser	Leu
15						1235					1240					1245
	Ile	Ser	Pro	Asp	Gly	Ser	Arg	Lys	Asn	Pro	Ala	Arg	Asn	Cys	Arg	Asp
20						1250					1255					1260
	Leu	Lys	Phe	Cys	His	Pro	Glu	Leu	Lys	Ser	Gly	Glu	Tyr	Trp	Val	Asp
	1265					1270					1275					1280
25	Pro	Asn	Gln	Gly	Cys	Lys	Leu	Asp	Ala	Ile	Lys	Val	Phe	Cys	Asn	Met
						1285					1290					1295
	Glu	Thr	Gly	Glu	Thr	Cys	Ile	Ser	Ala	Asn	Pro	Leu	Asn	Val	Pro	Arg
30						1300					1305					1310
	Lys	His	Trp	Trp	Thr	Asp	Ser	Ser	Ala	Glu	Lys	Lys	His	Val	Trp	Phe
35						1315					1320					1325
	Gly	Glu	Ser	Met	Asp	Gly	Gly	Phe	Gln	Phe	Ser	Tyr	Gly	Asn	Pro	Glu
	1330					1335					1340					
40	Leu	Pro	Glu	Asp	Val	Leu	Asp	Val	Gln	Leu	Ala	Phe	Leu	Arg	Leu	Leu
	1345					1350					1355					1360
45	Ser	Ser	Arg	Ala	Ser	Gln	Asn	Ile	Thr	Tyr	His	Cys	Lys	Asn	Ser	Ile
						1365					1370					1375
	Ala	Tyr	Met	Asp	Gln	Ala	Ser	Gly	Asn	Val	Lys	Lys	Ala	Leu	Lys	Leu
50						1380					1385					1390
	Met	Gly	Ser	Asn	Glu	Gly	Glu	Phe	Lys	Ala	Glu	Gly	Asn	Ser	Lys	Phe
						1395					1400					1405
55	Thr	Tyr	Thr	Val	Leu	Glu	Asp	Gly	Cys	Thr	Lys	His	Thr	Gly	Glu	Trp

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1410                      1415                      1420  
 Ser Lys Thr Val Phe Glu Tyr Arg Thr Arg Lys Ala Val Arg Leu Pro  
 5  
 1425                      1430                      1435                      1440  
 Ile Val Asp Ile Ala Pro Tyr Asp Ile Gly Gly Pro Asp Gln Glu Phe  
 10  
 1445                      1450                      1455  
 Gly Val Asp Val Gly Pro Val Cys Phe Leu  
 15  
 1460                      1465  
 15  
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 20  
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 25  
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 30  
 Met Val Leu Leu Thr Ala Val Leu Leu Leu Leu Ala Ala Tyr Ala Gly  
 1                      5                      10                      15  
 35  
 Pro Ala Gln Ser Leu Gly Ser Phe Val His Cys Glu Pro Cys Asp Glu  
 20                      25                      30  
 Lys Ala Leu Ser Met Cys Pro Pro Ser Pro Leu Gly Cys Glu Leu Val  
 40  
 35                      40                      45  
 Lys Glu Pro Gly Cys Gly Cys Cys Met Thr Cys Ala Leu Ala Glu Gly  
 50  
 50                      55                      60  
 45  
 Gln Ser Cys Gly Val Tyr Thr Glu Arg Cys Ala Gln Gly Leu Arg Cys  
 65                      70                      75                      80  
 50  
 Leu Pro Arg Gln Asp Glu Glu Lys Pro Leu His Ala Leu Leu His Gly  
 85                      90                      95  
 Arg Gly Val Cys Leu Asn Glu Lys Ser Tyr Arg Glu Gln Val Lys Ile  
 55  
 100                      105                      110

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Glu Arg Asp Ser Arg Glu His Glu Glu Pro Thr Thr Ser Glu Met Ala  
 115 120 125  
 5 Glu Glu Thr Tyr Ser Pro Lys Ile Phe Arg Pro Lys His Thr Arg Ile  
 130 135 140  
 10 Ser Glu Leu Lys Ala Glu Ala Val Lys Lys Asp Arg Arg Lys Lys Leu  
 145 150 155 160  
 Thr Gln Ser Lys Phe Val Gly Gly Ala Glu Asn Thr Ala His Pro Arg  
 15 165 170 175  
 Ile Ile Ser Ala Pro Glu Met Arg Gln Glu Ser Glu Gln Gly Pro Cys  
 180 185 190  
 20 Arg Arg His Met Glu Ala Ser Leu Gln Glu Leu Lys Ala Ser Pro Arg  
 195 200 205  
 25 Met Val Pro Arg Ala Val Tyr Leu Pro Asn Cys Asp Arg Lys Gly Phe  
 210 215 220  
 Tyr Lys Arg Lys Gln Cys Lys Pro Ser Arg Gly Arg Lys Arg Gly Ile  
 30 225 230 235 240  
 Cys Trp Cys Val Asp Lys Tyr Gly Met Lys Leu Pro Gly Met Glu Tyr  
 35 245 250 255  
 Val Asp Gly Asp Phe Gln Cys His Thr Phe Asp Ser Ser Asn Val Glu  
 260 265 270  
 40  
 45 <210> 105  
 <211> 158  
 <212> PRT  
 50 <213> Homo sapiens  
 <400> 105  
 55 Met Ala Ser Arg Ser Met Arg Leu Leu Leu Leu Leu Ser Cys Leu Ala

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1 5 10 15  
 5 Lys Thr Gly Val Leu Gly Asp Ile Ile Met Arg Pro Ser Cys Ala Pro  
 20 25 30  
 Gly Trp Phe Tyr His Lys Ser Asn Cys Tyr Gly Tyr Phe Arg Lys Leu  
 10 35 40 45  
 Arg Asn Trp Ser Asp Ala Glu Leu Glu Cys Gln Ser Tyr Gly Asn Gly  
 50 55 60  
 15 Ala His Leu Ala Ser Ile Leu Ser Leu Lys Glu Ala Ser Thr Ile Ala  
 65 70 75 80  
 20 Glu Tyr Ile Ser Gly Tyr Gln Arg Ser Gln Pro Ile Trp Ile Gly Leu  
 85 90 95  
 His Asp Pro Gln Lys Arg Gln Gln Trp Gln Trp Ile Asp Gly Ala Met  
 25 100 105 110  
 Tyr Leu Tyr Arg Ser Trp Ser Gly Lys Ser Met Gly Gly Asn Lys His  
 115 120 125  
 30 Cys Ala Glu Met Ser Ser Asn Asn Asn Phe Leu Thr Trp Ser Ser Asn  
 130 135 140  
 35 Glu Cys Asn Lys Arg Gln His Phe Leu Cys Lys Tyr Arg Pro  
 145 150 155  
 40  
 <210> 106  
 45 <211> 175  
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 50  
 <400> 106  
 55 Met Glu Lys Ile Pro Val Ser Ala Phe Leu Leu Leu Val Ala Leu Ser  
 1 5 10 15

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Tyr Thr Leu Ala Arg Asp Thr Thr Val Lys Pro Gly Ala Lys Lys Asp  
 5                   20                   25                   30  
 Thr Lys Asp Ser Arg Pro Lys Leu Pro Gln Thr Leu Ser Arg Gly Trp  
                   35                   40                   45  
 10 Gly Asp Gln Leu Ile Trp Thr Gln Thr Tyr Glu Glu Ala Leu Tyr Lys  
                   50                   55                   60  
 Ser Lys Thr Ser Asn Lys Pro Leu Met Ile Ile His His Leu Asp Glu  
 15                   65                   70                   75                   80  
 Cys Pro His Ser Gln Ala Leu Lys Lys Val Phe Ala Glu Asn Lys Glu  
 20                   85                   90                   95  
 Ile Gln Lys Leu Ala Glu Gln Phe Val Leu Leu Asn Leu Val Tyr Glu  
                   100                   105                   110  
 25 Thr Thr Asp Lys His Leu Ser Pro Asp Gly Gln Tyr Val Pro Arg Ile  
                   115                   120                   125  
 Met Phe Val Asp Pro Ser Leu Thr Val Arg Ala Asp Ile Thr Gly Arg  
 30                   130                   135                   140  
 Tyr Ser Asn Arg Leu Tyr Ala Tyr Glu Pro Ala Asp Thr Ala Leu Leu  
 35                   145                   150                   155                   160  
 Leu Asp Asn Met Lys Lys Ala Leu Lys Leu Leu Lys Thr Glu Leu  
                   165                   170                   175  
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 45 <210> 107  
      <211> 732  
      <212> PRT  
 50 <213> Homo sapiens  
  
 55 <400> 107  
 Met Pro Glu Glu Thr Gln Thr Gln Asp Gln Pro Met Glu Glu Glu Glu

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	1	5	10	15												
5	Val	Glu	Thr	Phe	Ala	Phe	Gln	Ala	Glu	Ile	Ala	Gln	Leu	Met	Ser	Leu
		20	25	30												
	Ile	Ile	Asn	Thr	Phe	Tyr	Ser	Asn	Lys	Glu	Ile	Phe	Leu	Arg	Glu	Leu
10		35	40	45												
	Ile	Ser	Asn	Ser	Ser	Asp	Ala	Leu	Asp	Lys	Ile	Arg	Tyr	Glu	Ser	Leu
		50	55	60												
15	Thr	Asp	Pro	Ser	Lys	Leu	Asp	Ser	Gly	Lys	Glu	Leu	His	Ile	Asn	Leu
	65		70							75					80	
20	Ile	Pro	Asn	Lys	Gln	Asp	Arg	Thr	Leu	Thr	Ile	Val	Asp	Thr	Gly	Ile
			85							90					95	
	Gly	Met	Thr	Lys	Ala	Asp	Leu	Ile	Asn	Asn	Leu	Gly	Thr	Ile	Ala	Lys
25		100								105					110	
	Ser	Gly	Thr	Lys	Ala	Phe	Met	Glu	Ala	Leu	Gln	Ala	Gly	Ala	Asp	Ile
		115								120					125	
30	Ser	Met	Ile	Gly	Gln	Phe	Gly	Val	Gly	Phe	Tyr	Ser	Ala	Tyr	Leu	Val
		130								135					140	
35	Ala	Glu	Lys	Val	Thr	Val	Ile	Thr	Lys	His	Asn	Asp	Asp	Glu	Gln	Tyr
	145					150						155			160	
	Ala	Trp	Glu	Ser	Ser	Ala	Gly	Gly	Ser	Phe	Thr	Val	Arg	Thr	Asp	Thr
40			165							170					175	
	Gly	Glu	Pro	Met	Gly	Arg	Gly	Thr	Lys	Val	Ile	Leu	His	Leu	Lys	Glu
		180								185					190	
45	Asp	Gln	Thr	Glu	Tyr	Leu	Glu	Glu	Arg	Arg	Ile	Lys	Glu	Ile	Val	Lys
		195								200					205	
50	Lys	His	Ser	Gln	Phe	Ile	Gly	Tyr	Pro	Ile	Thr	Leu	Phe	Val	Glu	Lys
		210								215					220	
	Glu	Arg	Asp	Lys	Glu	Val	Ser	Asp	Asp	Glu	Ala	Glu	Glu	Lys	Glu	Asp
55	225					230						235			240	



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Lys Glu Glu Glu Lys Glu Lys Glu Glu Lys Glu Ser Glu Asp Lys Pro  
 245 250 255  
 5 Glu Ile Glu Asp Val Gly Ser Asp Glu Glu Glu Lys Lys Asp Gly  
 260 265 270  
 10 Asp Lys Lys Lys Lys Lys Lys Ile Lys Glu Lys Tyr Ile Asp Gln Glu  
 275 280 285  
 Glu Leu Asn Lys Thr Lys Pro Ile Trp Thr Arg Asn Pro Asp Asp Ile  
 15 290 295 300  
 Thr Asn Glu Glu Tyr Gly Glu Phe Tyr Lys Ser Leu Thr Asn Asp Trp  
 20 305 310 315 320  
 Glu Asp His Leu Ala Val Lys His Phe Ser Val Glu Gly Gln Leu Glu  
 325 330 335  
 25 Phe Arg Ala Leu Leu Phe Val Pro Arg Arg Ala Pro Phe Asp Leu Phe  
 340 345 350  
 Glu Asn Arg Lys Lys Lys Asn Asn Ile Lys Leu Tyr Val Arg Arg Val  
 30 355 360 365  
 Phe Ile Met Asp Asn Cys Glu Glu Leu Ile Pro Glu Tyr Leu Asn Phe  
 35 370 375 380  
 Ile Arg Gly Val Val Asp Ser Glu Asp Leu Pro Leu Asn Ile Ser Arg  
 385 390 395 400  
 40 Glu Met Leu Gln Gln Ser Lys Ile Leu Lys Val Ile Arg Lys Asn Leu  
 405 410 415  
 Val Lys Lys Cys Leu Glu Leu Phe Thr Glu Leu Ala Glu Asp Lys Glu  
 45 420 425 430  
 Asn Tyr Lys Lys Phe Tyr Glu Gln Phe Ser Lys Asn Ile Lys Leu Gly  
 50 435 440 445  
 Ile His Glu Asp Ser Gln Asn Arg Lys Lys Leu Ser Glu Leu Leu Arg  
 450 455 460  
 55 Tyr Tyr Thr Ser Ala Ser Gly Asp Glu Met Val Ser Leu Lys Asp Tyr

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	465	470	475	480
5	Cys Thr Arg Met Lys Glu Asn Gln Lys His Ile Tyr Tyr Ile Thr Gly			
	485	490	495	
	Glu Thr Lys Asp Gln Val Ala Asn Ser Ala Phe Val Glu Arg Leu Arg			
10	500	505	510	
	Lys His Gly Leu Glu Val Ile Tyr Met Ile Glu Pro Ile Asp Glu Tyr			
	515	520	525	
15	Cys Val Gln Gln Leu Lys Glu Phe Glu Gly Lys Thr Leu Val Ser Val			
	530	535	540	
20	Thr Lys Glu Gly Leu Glu Leu Pro Glu Asp Glu Glu Glu Lys Lys Lys			
	545	550	555	560
	Gln Glu Glu Lys Lys Thr Lys Phe Glu Asn Leu Cys Lys Ile Met Lys			
25	565	570	575	
	Asp Ile Leu Glu Lys Lys Val Glu Lys Val Val Val Ser Asn Arg Leu			
	580	585	590	
30	Val Thr Ser Pro Cys Cys Ile Val Thr Ser Thr Tyr Gly Trp Thr Ala			
	595	600	605	
35	Asn Met Glu Arg Ile Met Lys Ala Gln Ala Leu Arg Asp Asn Ser Thr			
	610	615	620	
	Met Gly Tyr Met Ala Ala Lys Lys His Leu Glu Ile Asn Pro Asp His			
40	625	630	635	640
	Ser Ile Ile Glu Thr Leu Arg Gln Lys Ala Glu Ala Asp Lys Asn Asp			
	645	650	655	
45	Lys Ser Val Lys Asp Leu Val Ile Leu Leu Tyr Glu Thr Ala Leu Leu			
	660	665	670	
50	Ser Ser Gly Phe Ser Leu Glu Asp Pro Gln Thr His Ala Asn Arg Ile			
	675	680	685	
	Tyr Arg Met Ile Lys Leu Gly Leu Gly Ile Asp Glu Asp Asp Pro Thr			
55	690	695	700	

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Ala Asp Asp Thr Ser Ala Ala Val Thr Glu Glu Met Pro Pro Leu Glu  
5 705 710 715 720  
Gly Asp Asp Asp Thr Ser Arg Met Glu Glu Val Asp  
725 730  
10  
<210> 108  
15 <211> 1361  
<212> PRT  
20 <213> Homo sapiens  
  
<400> 108  
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1 5 10 15  
Ile Ser Trp Leu Thr Leu Thr Cys Phe Pro Gly Ala Thr Ser Thr Val  
30 20 25 30  
Ala Ala Gly Cys Pro Asp Gln Ser Pro Glu Leu Gln Pro Trp Asn Pro  
35 35 40 45  
Gly His Asp Gln Asp His His Val His Ile Gly Gln Gly Lys Thr Leu  
50 55 60  
40 Leu Leu Thr Ser Ser Ala Thr Val Tyr Ser Ile His Ile Ser Glu Gly  
65 70 75 80  
Gly Lys Leu Val Ile Lys Asp His Asp Glu Pro Ile Val Leu Arg Thr  
45 85 90 95  
Arg His Ile Leu Ile Asp Asn Gly Gly Glu Leu His Ala Gly Ser Ala  
50 100 105 110  
Leu Cys Pro Phe Gln Gly Asn Phe Thr Ile Ile Leu Tyr Gly Arg Ala  
115 120 125  
55 Asp Glu Gly Ile Gln Pro Asp Pro Tyr Tyr Gly Leu Lys Tyr Ile Gly

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	130		135		140	
5	Val Gly Lys Gly Gly Ala Leu Glu Leu His Gly Gln Lys Lys Leu Ser					
	145		150		155	160
	Trp Thr Phe Leu Asn Lys Thr Leu His Pro Gly Gly Met Ala Glu Gly					
10		165		170		175
	Gly Tyr Phe Phe Glu Arg Ser Trp Gly His Arg Gly Val Ile Val His					
		180		185		190
15	Val Ile Asp Pro Lys Ser Gly Thr Val Ile His Ser Asp Arg Phe Asp					
		195		200		205
20	Thr Tyr Arg Ser Lys Lys Glu Ser Glu Arg Leu Val Gln Tyr Leu Asn					
		210		215		220
	Ala Val Pro Asp Gly Arg Ile Leu Ser Val Ala Val Asn Asp Glu Gly					
25		225		230		235
						240
	Ser Arg Asn Leu Asp Asp Met Ala Arg Lys Ala Met Thr Lys Leu Gly					
		245		250		255
30	Ser Lys His Phe Leu His Leu Gly Phe Arg His Pro Trp Ser Phe Leu					
		260		265		270
35	Thr Val Lys Gly Asn Pro Ser Ser Ser Val Glu Asp His Ile Glu Tyr					
		275		280		285
	His Gly His Arg Gly Ser Ala Ala Ala Arg Val Phe Lys Leu Phe Gln					
40		290		295		300
	Thr Glu His Gly Glu Tyr Phe Asn Val Ser Leu Ser Ser Glu Trp Val					
45		305		310		315
						320
	Gln Asp Val Glu Trp Thr Glu Trp Phe Asp His Asp Lys Val Ser Gln					
		325		330		335
50	Thr Lys Gly Gly Glu Lys Ile Ser Asp Leu Trp Lys Ala His Pro Gly					
		340		345		350
	Lys Ile Cys Asn Arg Pro Ile Asp Ile Gln Ala Thr Thr Met Asp Gly					
55		355		360		365

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Val Asn Leu Ser Thr Glu Val Val Tyr Lys Lys Gly Gln Asp Tyr Arg  
370 375 380  
5 Phe Ala Cys Tyr Asp Arg Gly Arg Ala Cys Arg Ser Tyr Arg Val Arg  
385 390 395 400  
10 Phe Leu Cys Gly Lys Pro Val Arg Pro Lys Leu Thr Val Thr Ile Asp  
405 410 415  
Thr Asn Val Asn Ser Thr Ile Leu Asn Leu Glu Asp Asn Val Gln Ser  
15 420 425 430  
Trp Lys Pro Gly Asp Thr Leu Val Ile Ala Ser Thr Asp Tyr Ser Met  
20 435 440 445  
Tyr Gln Ala Glu Glu Phe Gln Val Leu Pro Cys Arg Ser Cys Ala Pro  
450 455 460  
25 Asn Gln Val Lys Val Ala Gly Lys Pro Met Tyr Leu His Ile Gly Glu  
465 470 475 480  
Glu Ile Asp Gly Val Asp Met Arg Ala Glu Val Gly Leu Leu Ser Arg  
30 485 490 495  
Asn Ile Ile Val Met Gly Glu Met Glu Asp Lys Cys Tyr Pro Tyr Arg  
35 500 505 510  
Asn His Ile Cys Asn Phe Phe Asp Phe Asp Thr Phe Gly Gly His Ile  
515 520 525  
40 Lys Phe Ala Leu Gly Phe Lys Ala Ala His Leu Glu Gly Thr Glu Leu  
530 535 540  
Lys His Met Gly Gln Gln Leu Val Gly Gln Tyr Pro Ile His Phe His  
45 545 550 555 560  
Leu Ala Gly Asp Val Asp Glu Arg Gly Gly Tyr Asp Pro Pro Thr Tyr  
50 565 570 575  
Ile Arg Asp Leu Ser Ile His His Thr Phe Ser Arg Cys Val Thr Val  
580 585 590  
55 His Gly Ser Asn Gly Leu Leu Ile Lys Asp Val Val Gly Tyr Asn Ser

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	595	600	605
5	Leu Gly His Cys Phe Phe Thr Glu Asp Gly Pro Glu Glu Arg Asn Thr		
	610	615	620
	Phe Asp His Cys Leu Gly Leu Leu Val Lys Ser Gly Thr Leu Leu Pro		
10	625	630	635
	Ser Asp Arg Asp Ser Lys Met Cys Lys Met Ile Thr Glu Asp Ser Tyr		
	645	650	655
15	Pro Gly Tyr Ile Pro Lys Pro Arg Gln Asp Cys Asn Ala Val Ser Thr		
	660	665	670
20	Phe Trp Met Ala Asn Pro Asn Asn Asn Leu Ile Asn Cys Ala Ala Ala		
	675	680	685
	Gly Ser Glu Glu Thr Gly Phe Trp Phe Ile Phe His His Val Pro Thr		
25	690	695	700
	Gly Pro Ser Val Gly Met Tyr Ser Pro Gly Tyr Ser Glu His Ile Pro		
	705	710	715
30	Leu Gly Lys Phe Tyr Asn Asn Arg Ala His Ser Asn Tyr Arg Ala Gly		
	725	730	735
35	Met Ile Ile Asp Asn Gly Val Lys Thr Thr Glu Ala Ser Ala Lys Asp		
	740	745	750
	Lys Arg Pro Phe Leu Ser Ile Ile Ser Ala Arg Tyr Ser Pro His Gln		
40	755	760	765
	Asp Ala Asp Pro Leu Lys Pro Arg Glu Pro Ala Ile Ile Arg His Phe		
	770	775	780
45	Ile Ala Tyr Lys Asn Gln Asp His Gly Ala Trp Leu Arg Gly Gly Asp		
	785	790	795
	Val Trp Leu Asp Ser Cys Arg Phe Ala Asp Asn Gly Ile Gly Leu Thr		
50	805	810	815
	Leu Ala Ser Gly Gly Thr Phe Pro Tyr Asp Asp Gly Ser Lys Gln Glu		
55	820	825	830

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Ile Lys Asn Ser Leu Phe Val Gly Glu Ser Gly Asn Val Gly Thr Glu  
5 835 840 845  
Met Met Asp Asn Arg Ile Trp Gly Pro Gly Gly Leu Asp His Ser Gly  
850 855 860  
10 Arg Thr Leu Pro Ile Gly Gln Asn Phe Pro Ile Arg Gly Ile Gln Leu  
865 870 875 880  
Tyr Asp Gly Pro Ile Asn Ile Gln Asn Cys Thr Phe Arg Lys Phe Val  
15 885 890 895  
Ala Leu Glu Gly Arg His Thr Ser Ala Leu Ala Phe Arg Leu Asn Asn  
900 905 910  
20 Ala Trp Gln Ser Cys Pro His Asn Asn Val Thr Gly Ile Ala Phe Glu  
915 920 925  
25 Asp Val Pro Ile Thr Ser Arg Val Phe Phe Gly Glu Pro Gly Pro Trp  
930 935 940  
Phe Asn Gln Leu Asp Met Asp Gly Asp Lys Thr Ser Val Phe His Asp  
30 945 950 955 960  
Val Asp Gly Ser Val Ser Glu Tyr Pro Gly Ser Tyr Leu Thr Lys Asn  
965 970 975  
35 Asp Asn Trp Leu Val Arg His Pro Asp Cys Ile Asn Val Pro Asp Trp  
980 985 990  
40 Arg Gly Ala Ile Cys Ser Gly Cys Tyr Ala Gln Met Tyr Ile Gln Ala  
995 1000 1005  
Tyr Lys Thr Ser Asn Leu Arg Met Lys Ile Ile Lys Asn Asp Phe Pro  
45 1010 1015 1020  
Ser His Pro Leu Tyr Leu Glu Gly Ala Leu Thr Arg Ser Thr His Tyr  
1025 1030 1035 1040  
50 Gln Gln Tyr Gln Pro Val Val Thr Leu Gln Lys Gly Tyr Thr Ile His  
1045 1050 1055  
55 Trp Asp Gln Thr Ala Pro Ala Glu Leu Ala Ile Trp Leu Ile Asn Phe

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	1060	1065	1070
5	Asn Lys Gly Asp Trp Ile Arg Val Gly Leu Cys Tyr Pro Arg Gly Thr		
	1075	1080	1085
	Thr Phe Ser Ile Leu Ser Asp Val His Asn Arg Leu Leu Lys Gln Thr		
10	1090	1095	1100
	Ser Lys Thr Gly Val Phe Val Arg Thr Leu Gln Met Asp Lys Val Glu		
	1105	1110	1115
15	Gln Ser Tyr Pro Gly Arg Ser His Tyr Tyr Trp Asp Glu Asp Ser Gly		
	1125	1130	1135
	Leu Leu Phe Leu Lys Leu Lys Ala Gln Asn Glu Arg Glu Lys Phe Ala		
20	1140	1145	1150
	Phe Cys Ser Met Lys Gly Cys Glu Arg Ile Lys Ile Lys Ala Leu Ile		
25	1155	1160	1165
	Pro Lys Asn Ala Gly Val Ser Asp Cys Thr Ala Thr Ala Tyr Pro Lys		
	1170	1175	1180
30	Phe Thr Glu Arg Ala Val Val Asp Val Pro Met Pro Lys Lys Leu Phe		
	1185	1190	1195
	Gly Ser Gln Leu Lys Thr Lys Asp His Phe Leu Glu Val Lys Met Glu		
35	1205	1210	1215
	Ser Ser Lys Gln His Phe Phe His Leu Trp Asn Asp Phe Ala Tyr Ile		
40	1220	1225	1230
	Glu Val Asp Gly Lys Lys Tyr Pro Ser Ser Glu Asp Gly Ile Gln Val		
	1235	1240	1245
45	Val Val Ile Asp Gly Asn Gln Gly Arg Val Val Ser His Thr Ser Phe		
	1250	1255	1260
	Arg Asn Ser Ile Leu Gln Gly Ile Pro Trp Gln Leu Phe Asn Tyr Val		
50	1265	1270	1275
	Ala Thr Ile Pro Asp Asn Ser Ile Val Leu Met Ala Ser Lys Gly Arg		
55	1285	1290	1295



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Tyr Val Ser Arg Gly Pro Trp Thr Arg Val Leu Glu Lys Leu Gly Ala  
 1300 1305 1310  
 5 Asp Arg Gly Leu Lys Leu Lys Glu Gln Met Ala Phe Val Gly Phe Lys  
 1315 1320 1325  
 10 Gly Ser Phe Arg Pro Ile Trp Val Thr Leu Asp Thr Glu Asp His Lys  
 1330 1335 1340  
 Ala Lys Ile Phe Gln Val Val Pro Ile Pro Val Val Lys Lys Lys Lys  
 15 1345 1350 1355 1360  
 Leu  
 20  
 25 <210> 109  
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 30 <213> Homo sapiens  
 35 <400> 109  
 Met His Ser Phe Pro Pro Leu Leu Leu Leu Leu Phe Trp Gly Val Val  
 1 5 10 15  
 40 Ser His Ser Phe Pro Ala Thr Leu Glu Thr Gln Glu Gln Asp Val Asp  
 20 25 30  
 Leu Val Gln Lys Tyr Leu Glu Lys Tyr Tyr Asn Leu Lys Asn Asp Gly  
 45 35 40 45  
 Arg Gln Val Glu Lys Arg Arg Asn Ser Gly Pro Val Val Glu Lys Leu  
 50 55 60  
 50 Lys Gln Met Gln Glu Phe Phe Gly Leu Lys Val Thr Gly Lys Pro Asp  
 65 70 75 80  
 55 Ala Glu Thr Leu Lys Val Met Lys Gln Pro Arg Cys Gly Val Pro Asp

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	85	90	95
5	Val Ala Gln Phe Val Leu Thr Glu Gly Asn Pro Arg Trp Glu Gln Thr		
	100	105	110
	His Leu Thr Tyr Arg Ile Glu Asn Tyr Thr Pro Asp Leu Pro Arg Ala		
10	115	120	125
	Asp Val Asp His Ala Ile Glu Lys Ala Phe Gln Leu Trp Ser Asn Val		
	130	135	140
15	Thr Pro Leu Thr Phe Thr Lys Val Ser Glu Gly Gln Ala Asp Ile Met		
	145	150	155
	Ile Ser Phe Val Arg Gly Asp His Arg Asp Asn Ser Pro Phe Asp Gly		
20	165	170	175
	Pro Gly Gly Asn Leu Ala His Ala Phe Gln Pro Gly Pro Gly Ile Gly		
25	180	185	190
	Gly Asp Ala His Phe Asp Glu Asp Glu Arg Trp Thr Asn Asn Phe Arg		
	195	200	205
30	Glu Tyr Asn Leu His Arg Val Ala Ala His Glu Leu Gly His Ser Leu		
	210	215	220
	Gly Leu Ser His Ser Thr Asp Ile Gly Ala Leu Met Tyr Pro Ser Tyr		
35	225	230	235
	Thr Phe Ser Gly Asp Val Gln Leu Ala Gln Asp Asp Ile Asp Gly Ile		
40	245	250	255
	Gln Ala Ile Tyr Gly Arg Ser Gln Asn Pro Val Gln Pro Ile Gly Pro		
	260	265	270
45	Gln Thr Pro Lys Ala Cys Asp Ser Lys Leu Thr Phe Asp Ala Ile Thr		
	275	280	285
	Thr Ile Arg Gly Glu Val Met Phe Phe Lys Asp Arg Phe Tyr Met Arg		
50	290	295	300
	Thr Asn Pro Phe Tyr Pro Glu Val Glu Leu Asn Phe Ile Ser Val Phe		
55	305	310	315
			320

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Trp Pro Gln Leu Pro Asn Gly Leu Glu Ala Ala Tyr Glu Phe Ala Asp  
325 330 335  
5 Arg Asp Glu Val Arg Phe Phe Lys Gly Asn Lys Tyr Trp Ala Val Gln  
340 345 350  
10 Gly Gln Asn Val Leu His Gly Tyr Pro Lys Asp Ile Tyr Ser Ser Phe  
355 360 365  
Gly Phe Pro Arg Thr Val Lys His Ile Asp Ala Ala Leu Ser Glu Glu  
15 370 375 380  
Asn Thr Gly Lys Thr Tyr Phe Phe Val Ala Asn Lys Tyr Trp Arg Tyr  
385 390 395 400  
20 Asp Glu Tyr Lys Arg Ser Met Asp Pro Gly Tyr Pro Lys Met Ile Ala  
405 410 415  
25 His Asp Phe Pro Gly Ile Gly His Lys Val Asp Ala Val Phe Met Lys  
420 425 430  
Asp Gly Phe Phe Tyr Phe Phe His Gly Thr Arg Gln Tyr Lys Phe Asp  
30 435 440 445  
Pro Lys Thr Lys Arg Ile Leu Thr Leu Gln Lys Ala Asn Ser Trp Phe  
450 455 460  
35 Asn Cys Arg Lys Asn  
465  
40  
<210> 110  
45 <211> 267  
<212> PRT  
<213> Homo sapiens  
50  
<400> 110  
55 Met Arg Leu Thr Val Leu Cys Ala Val Cys Leu Leu Pro Gly Ser Leu

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	1	5	10	15												
5	Ala	Leu	Pro	Leu	Pro	Gln	Glu	Ala	Gly	Gly	Met	Ser	Glu	Leu	Gln	Trp
				20					25					30		
	Glu	Gln	Ala	Gln	Asp	Tyr	Leu	Lys	Arg	Phe	Tyr	Leu	Tyr	Asp	Ser	Glu
10				35					40					45		
	Thr	Lys	Asn	Ala	Asn	Ser	Leu	Glu	Ala	Lys	Leu	Lys	Glu	Met	Gln	Lys
				50					55					60		
15	Phe	Phe	Gly	Leu	Pro	Ile	Thr	Gly	Met	Leu	Asn	Ser	Arg	Val	Ile	Glu
				65					70					75		80
20	Ile	Met	Gln	Lys	Pro	Arg	Cys	Gly	Val	Pro	Asp	Val	Ala	Glu	Tyr	Ser
								85					90			95
	Leu	Phe	Pro	Asn	Ser	Pro	Lys	Trp	Thr	Ser	Lys	Val	Val	Thr	Tyr	Arg
25				100					105					110		
	Ile	Val	Ser	Tyr	Thr	Arg	Asp	Leu	Pro	His	Ile	Thr	Val	Asp	Arg	Leu
				115					120					125		
30	Val	Ser	Lys	Ala	Leu	Asn	Met	Trp	Gly	Lys	Glu	Ile	Pro	Leu	His	Phe
				130					135					140		
35	Arg	Lys	Val	Val	Trp	Gly	Thr	Ala	Asp	Ile	Met	Ile	Gly	Phe	Ala	Arg
				145					150				155			160
	Gly	Ala	His	Gly	Asp	Ser	Tyr	Pro	Phe	Asp	Gly	Pro	Gly	Asn	Thr	Leu
40				165					170					175		
	Ala	His	Ala	Phe	Ala	Pro	Gly	Thr	Gly	Leu	Gly	Gly	Asp	Ala	His	Phe
				180					185					190		
45	Asp	Glu	Asp	Glu	Arg	Trp	Thr	Asp	Gly	Ser	Ser	Leu	Gly	Ile	Asn	Phe
				195					200					205		
50	Leu	Tyr	Ala	Ala	Thr	His	Glu	Leu	Gly	His	Ser	Leu	Gly	Met	Gly	His
				210					215					220		
	Ser	Ser	Asp	Pro	Asn	Ala	Val	Met	Tyr	Pro	Thr	Tyr	Gly	Asn	Gly	Asp
55				225					230					235		240

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Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys  
245 250 255  
5  
Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys  
260 265  
10  
<210> 111  
15  
<211> 216  
<212> PRT  
<213> Homo sapiens  
20  
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Met Arg Pro Arg Ser Gly Pro Thr Arg Asn Pro Arg Leu Arg Ala Phe  
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Ala Gly Val Pro Thr Arg Gly Arg Thr Arg Gly Gln Ser Arg Arg Cys  
30 20 25 30  
Ala Ala Glu Ala Ser Ala Gly Pro Glu Arg Asp Ala Arg Pro Gly Ala  
35 35 40 45  
Pro Ala Ala Gly Thr Met Gly Ala Ala His Ser Ala Ser Glu Glu Val  
50 55 60  
40  
Arg Glu Leu Glu Gly Lys Thr Gly Phe Ser Ser Asp Gln Ile Glu Gln  
65 70 75 80  
Leu His Arg Arg Phe Lys Gln Leu Ser Gly Asp Gln Pro Thr Ile Arg  
45 85 90 95  
Lys Glu Asn Phe Asn Asn Val Pro Asp Leu Glu Leu Asn Pro Ile Arg  
100 105 110  
50  
Ser Lys Ile Val Arg Ala Phe Phe Asp Asn Arg Asn Leu Arg Lys Gly  
115 120 125  
55  
Pro Ser Gly Leu Ala Asp Glu Ile Asn Phe Glu Asp Phe Leu Thr Ile

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130 135 140  
 5 Met Ser Tyr Phe Arg Pro Ile Asp Thr Thr Met Asp Glu Glu Gln Val  
 145 150 155 160  
 Glu Leu Ser Arg Lys Glu Lys Leu Arg Phe Leu Phe His Met Tyr Asp  
 10 165 170 175  
 Ser Asp Ser Asp Gly Arg Ile Thr Leu Glu Glu Tyr Arg Asn Val Lys  
 15 180 185 190  
 Trp Ser Arg Ser Cys Cys Arg Glu Thr Leu Thr Ser Arg Arg Ser Pro  
 195 200 205  
 20 Leu Ala Pro Ser Pro Thr Gly Pro  
 210 215  
 25  
 <210> 112  
 <211> 422  
 30 <212> PRT  
 <213> Homo sapiens  
 35  
 <400> 112  
 Met Asn Ser Gly His Ser Phe Ser Gln Thr Pro Ser Ala Ser Phe His  
 40 1 5 10 15  
 Gly Ala Gly Gly Gly Trp Gly Arg Pro Arg Ser Phe Pro Arg Ala Pro  
 20 25 30  
 45 Thr Val His Gly Gly Ala Gly Gly Ala Arg Ile Ser Leu Ser Phe Thr  
 35 40 45  
 Thr Arg Ser Cys Pro Pro Pro Gly Gly Ser Trp Gly Ser Gly Arg Ser  
 50 50 55 60  
 Ser Pro Leu Leu Gly Gly Asn Gly Lys Ala Thr Met Gln Asn Leu Asn  
 55 65 70 75 80

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Asp Arg Leu Ala Ser Tyr Val Glu Lys Val Arg Ala Leu Glu Glu Ala  
 5                               85                               90                               95  
 Asn Met Lys Leu Glu Ser Arg Ile Leu Lys Trp His Gln Gln Arg Asp  
                               100                               105                               110  
 10 Pro Gly Ser Lys Lys Asp Tyr Ser Gln Tyr Glu Glu Asn Ile Thr His  
                               115                               120                               125  
 Leu Gln Glu Gln Ile Val Asp Gly Lys Met Thr Asn Ala Gln Ile Ile  
 15                               130                               135                               140  
 Leu Leu Ile Asp Asn Ala Arg Met Ala Val Asp Asp Phe Asn Leu Lys  
 20 145                               150                               155                               160  
 Tyr Glu Asn Glu His Ser Phe Lys Lys Asp Leu Glu Ile Glu Val Glu  
                               165                               170                               175  
 25 Gly Leu Arg Arg Thr Leu Asp Asn Leu Thr Ile Val Thr Thr Asp Leu  
                               180                               185                               190  
 Glu Gln Glu Val Glu Gly Met Arg Lys Glu Leu Ile Leu Met Lys Lys  
 30                               195                               200                               205  
 His His Glu Gln Glu Met Glu Lys His His Val Pro Ser Asp Phe Asn  
 35                               210                               215                               220  
 Val Asn Val Lys Val Asp Thr Gly Pro Arg Glu Asp Leu Ile Lys Val  
 225                               230                               235                               240  
 40 Leu Glu Asp Met Arg Gln Glu Tyr Glu Leu Ile Ile Lys Lys Lys His  
                               245                               250                               255  
 Arg Asp Leu Asp Thr Trp Tyr Lys Glu Gln Ser Ala Ala Met Ser Gln  
 45                               260                               265                               270  
 Glu Ala Ala Ser Pro Ala Thr Val Gln Ser Arg Gln Gly Asp Ile His  
 50                               275                               280                               285  
 Glu Leu Lys Arg Thr Phe Gln Ala Leu Glu Ile Asp Leu Gln Thr Gln  
                               290                               295                               300  
 55 Tyr Ser Thr Lys Ser Ala Leu Glu Asn Met Leu Ser Glu Thr Gln Ser

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305                      310                      315                      320  
 5    Arg Tyr Ser Cys Lys Leu Gln Asp Met Gln Glu Ile Ile Ser His Tyr  
                          325                      330                      335  
 Glu Glu Glu Leu Thr Gln Leu Arg His Glu Leu Glu Arg Gln Asn Asn  
 10                      340                      345                      350  
 Glu Tyr Gln Val Leu Leu Gly Ile Lys Thr His Leu Glu Lys Glu Ile  
                          355                      360                      365  
 15    Thr Thr Tyr Arg Arg Leu Leu Glu Gly Glu Ser Glu Gly Thr Arg Glu  
                          370                      375                      380  
 Glu Ser Lys Ser Ser Met Lys Val Phe Ala Thr Pro Lys Ile Lys Ala  
 20    385                      390                      395                      400  
 Ile Thr Gln Glu Thr Ile Asn Gly Arg Leu Val Leu Cys Gln Val Asn  
 25                      405                      410                      415  
 Glu Ile Gln Lys His Ala  
                          420  
 30  
 <210> 113  
 35    <211> 398  
          <212> PRT  
 40    <213> Homo sapiens  
 <400> 113  
 45    Met Met Leu Lys Gly Ile Thr Arg Leu Ile Ser Arg Ile His Lys Leu  
          1                      5                      10                      15  
 Asp Pro Gly Arg Phe Leu His Met Gly Thr Gln Ala Arg Gln Ser Ile  
 50                      20                      25                      30  
 Ala Ala His Leu Asp Asn Gln Val Pro Val Glu Ser Pro Arg Ala Ile  
 55                      35                      40                      45



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Ser Arg Thr Asn Glu Asn Asp Pro Ala Lys His Gly Asp Gln His Glu  
5           50                           55                           60  
Gly Gln His Tyr Asn Ile Ser Pro Gln Asp Leu Glu Thr Val Phe Pro  
65                           70                           75                           80  
10 His Gly Leu Pro Pro Arg Phe Val Met Gln Val Lys Thr Phe Ser Glu  
                         85                           90                           95  
Ala Cys Leu Met Val Arg Lys Pro Ala Leu Glu Leu Leu His Tyr Leu  
15                           100                           105                           110  
Lys Asn Thr Ser Phe Ala Tyr Pro Ala Ile Arg Tyr Leu Leu Tyr Gly  
20                           115                           120                           125  
Glu Lys Gly Thr Gly Lys Thr Leu Ser Leu Cys His Val Ile His Phe  
                         130                           135                           140  
25 Cys Ala Lys Gln Asp Trp Leu Ile Leu His Ile Pro Asp Ala His Leu  
145                           150                           155                           160  
Trp Val Lys Asn Cys Arg Asp Leu Leu Gln Ser Ser Tyr Asn Lys Gln  
30                           165                           170                           175  
Arg Phe Asp Gln Pro Leu Glu Ala Ser Thr Trp Leu Lys Asn Phe Lys  
                         180                           185                           190  
35 Thr Thr Asn Glu Arg Phe Leu Asn Gln Ile Lys Val Gln Glu Lys Tyr  
                         195                           200                           205  
40 Val Trp Asn Lys Arg Glu Ser Thr Glu Lys Gly Ser Pro Leu Gly Glu  
                         210                           215                           220  
Val Val Glu Gln Gly Ile Thr Arg Val Arg Asn Ala Thr Asp Ala Val  
45                           225                           230                           235                           240  
Gly Ile Val Leu Lys Glu Leu Lys Arg Gln Ser Ser Leu Gly Met Phe  
                         245                           250                           255  
50 His Leu Leu Val Ala Val Asp Gly Ile Asn Ala Leu Trp Gly Arg Thr  
                         260                           265                           270  
55 Thr Leu Lys Arg Glu Asp Lys Ser Pro Ile Ala Pro Glu Glu Leu Ala

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275                      280                      285  
 5      Leu Val His Asn Leu Arg Lys Met Met Lys Asn Asp Trp His Gly Gly  
          290                      295                      300  
     Ala Ile Val Ser Ala Leu Ser Gln Thr Gly Ser Leu Phe Lys Pro Arg  
 10      305                      310                      315                      320  
     Lys Ala Tyr Leu Pro Gln Glu Leu Leu Gly Lys Glu Gly Phe Asp Ala  
                          325                      330                      335  
 15      Leu Asp Pro Phe Ile Pro Ile Leu Val Ser Asn Tyr Asn Pro Lys Glu  
                          340                      345                      350  
 20      Phe Glu Ser Cys Ile Gln Tyr Tyr Leu Glu Asn Asn Trp Leu Gln His  
                          355                      360                      365  
     Glu Lys Ala Pro Thr Glu Glu Gly Lys Lys Glu Leu Leu Phe Leu Ser  
 25      370                      375                      380  
     Asn Ala Asn Pro Ser Leu Leu Glu Arg His Cys Ala Tyr Leu  
     385                      390                      395  
 30  
  
 35      <210> 114  
          <211> 75  
          <212> PRT  
 40      <213> Homo sapiens  
  
          <400> 114  
 45      Met Leu Ser His Phe Arg Val Lys Val Lys Gly Phe Ile Leu Ile Ser  
          1                      5                      10                      15  
 50      Lys Tyr Phe Asp Pro Tyr Asp Leu Val Ser Ser Tyr Pro Lys Tyr Gly  
                          20                      25                      30  
     Pro His Thr Ser Arg Thr Gly Ile Leu Trp Glu Leu Val Arg Asn Val  
 55      35                      40                      45

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Glu Ser Leu Val Leu Arg Phe Ser Lys Ser Glu Ser Ala Phe Ser Ser  
5                   50                               55                               60  
Ala Leu Leu Ala Ile His Met Phe Glu Lys Asp  
65                               70                               75  
10  
<210> 115  
15  
<211> 163  
<212> PRT  
20  
<213> Homo sapiens  
  
<400> 115  
25  
Met Ser Glu Ser Gly Phe Lys Leu Leu Cys Gln Cys Leu Gly Phe Gly  
1                               5                               10                               15  
Ser Gly His Phe Arg Cys Asp Ser Ser Arg Trp Cys His Asp Asn Gly  
30                               20                               25                               30  
Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp Arg Gln Gly Glu Asn Gly  
35                               35                               40                               45  
Gln Met Met Ser Cys Thr Cys Leu Gly Asn Gly Lys Gly Glu Phe Lys  
50                               55                               60  
40  
Cys Asp Pro His Glu Ala Thr Cys Tyr Asp Asp Gly Lys Thr Tyr His  
65                               70                               75                               80  
Val Gly Glu Gln Trp Gln Lys Glu Tyr Leu Gly Ala Ile Cys Ser Cys  
45                               85                               90                               95  
Thr Cys Phe Gly Gly Gln Arg Gly Trp Arg Cys Asp Asn Cys Arg Arg  
100                               105                               110  
50  
Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr Gly Gln Ser Tyr Asn  
115                               120                               125  
55  
Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn Thr Asn Val Asn Cys

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	130	135	140
5	Pro Ile Glu Cys Phe Met Pro Leu Asp Val Gln Ala Asp Arg Glu Asp		
	145	150	155
	Ser Arg Glu		
10			
15	<210> 116		
	<211> 483		
	<212> PRT		
20	<213> Homo sapiens		
25	<400> 116		
	Met Ser Ile Arg Val Thr Gln Lys Ser Tyr Lys Val Ser Thr Ser Gly		
	1 5 10 15		
30	Pro Arg Ala Phe Ser Ser Arg Ser Tyr Thr Ser Gly Pro Gly Ser Arg		
	20 25 30		
	Ile Ser Ser Ser Ser Phe Ser Arg Val Gly Ser Ser Asn Phe Arg Gly		
35	35 40 45		
	Gly Leu Gly Gly Gly Tyr Gly Gly Ala Ser Gly Met Gly Gly Ile Thr		
40	50 55 60		
	Ala Val Thr Val Asn Gln Ser Leu Leu Ser Pro Leu Val Leu Glu Val		
	65 70 75 80		
45	Asp Pro Asn Ile Gln Ala Val Arg Thr Gln Glu Lys Glu Gln Ile Lys		
	85 90 95		
	Thr Leu Asn Asn Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu		
50	100 105 110		
	Glu Gln Gln Asn Lys Met Leu Glu Thr Lys Trp Ser Leu Leu Gln Gln		
55	115 120 125		

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Gln Lys Thr Ala Arg Ser Asn Met Asp Asn Met Phe Glu Ser Tyr Ile  
130 135 140  
5 Asn Asn Leu Arg Arg Gln Leu Glu Thr Leu Gly Gln Glu Lys Leu Lys  
145 150 155 160  
10 Leu Glu Ala Glu Leu Gly Asn Met Gln Gly Leu Val Glu Asp Phe Lys  
165 170 175  
Asn Lys Tyr Glu Asp Glu Ile Asn Lys Arg Thr Glu Met Glu Asn Glu  
15 180 185 190  
Phe Val Leu Ile Lys Lys Asp Val Asp Glu Ala Tyr Met Asn Lys Val  
195 200 205  
20 Glu Leu Glu Ser Arg Leu Glu Gly Leu Thr Asp Glu Ile Asn Phe Leu  
210 215 220  
25 Arg Gln Leu Tyr Glu Glu Glu Ile Arg Glu Leu Gln Ser Gln Ile Ser  
225 230 235 240  
Asp Thr Ser Val Val Leu Ser Met Asp Asn Ser Arg Ser Leu Asp Met  
30 245 250 255  
Asp Ser Ile Ile Ala Glu Val Lys Ala Gln Tyr Glu Asp Ile Ala Asn  
260 265 270  
35 Arg Ser Arg Ala Glu Ala Glu Ser Met Tyr Gln Ile Lys Tyr Glu Glu  
275 280 285  
40 Leu Gln Ser Leu Ala Gly Lys His Gly Asp Asp Leu Arg Arg Thr Lys  
290 295 300  
Thr Glu Ile Ser Glu Met Asn Arg Asn Ile Ser Arg Leu Gln Ala Glu  
45 305 310 315 320  
Ile Glu Gly Leu Lys Gly Gln Arg Ala Ser Leu Glu Ala Ala Ile Ala  
325 330 335  
50 Asp Ala Glu Gln Arg Gly Glu Leu Ala Ile Lys Asp Ala Asn Ala Lys  
340 345 350  
55 Leu Ser Glu Leu Glu Ala Ala Leu Gln Arg Ala Lys Gln Asp Met Ala

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355 360 365  
 5 Arg Gln Leu Arg Glu Tyr Gln Glu Leu Met Asn Val Lys Leu Ala Leu  
 370 375 380  
 Asp Ile Glu Ile Ala Thr Tyr Arg Lys Leu Leu Glu Gly Glu Glu Ser  
 10 385 390 395 400  
 Arg Leu Glu Ser Gly Met Gln Asn Met Ser Ile His Thr Lys Thr Thr  
 405 410 415  
 15 Ser Gly Tyr Ala Gly Gly Leu Ser Ser Ala Tyr Gly Gly Leu Thr Ser  
 420 425 430  
 20 Pro Gly Leu Ser Tyr Ser Leu Gly Ser Ser Phe Gly Ser Gly Ala Gly  
 435 440 445  
 Ser Ser Ser Phe Ser Arg Thr Ser Ser Ser Arg Ala Val Val Val Lys  
 25 450 455 460  
 Lys Ile Glu Thr Arg Asp Gly Lys Leu Val Ser Glu Ser Ser Asp Val  
 465 470 475 480  
 30 Leu Pro Lys

35

<210> 117

40

<211> 430

<212> PRT

<213> Homo sapiens

45

<400> 117

50 Met Ser Phe Thr Thr Arg Ser Thr Phe Ser Thr Asn Tyr Arg Ser Leu  
 1 5 10 15  
 Gly Ser Val Gln Ala Pro Ser Tyr Gly Ala Arg Pro Val Ser Ser Ala

55

20

25

30

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Ala Ser Val Tyr Ala Gly Ala Gly Gly Ser Gly Ser Arg Ile Ser Val  
35 40 45  
5 Ser Arg Ser Thr Ser Phe Arg Gly Gly Met Gly Ser Gly Gly Leu Ala  
50 55 60  
10 Thr Gly Ile Ala Gly Gly Leu Ala Gly Met Gly Gly Ile Gln Asn Glu  
65 70 75 80  
Lys Glu Thr Met Gln Ser Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp  
15 85 90 95  
Arg Val Arg Ser Leu Glu Thr Glu Asn Arg Arg Leu Glu Ser Lys Ile  
100 105 110  
20 Arg Glu His Leu Glu Lys Lys Gly Pro Gln Val Arg Asp Trp Ser His  
115 120 125  
25 Tyr Phe Lys Ile Ile Glu Asp Leu Arg Ala Gln Ile Phe Ala Asn Thr  
130 135 140  
Val Asp Asn Ala Arg Ile Val Leu Gln Ile Asp Asn Ala Arg Leu Ala  
30 145 150 155 160  
Ala Asp Asp Phe Arg Val Lys Tyr Glu Thr Glu Leu Ala Met Arg Gln  
165 170 175  
35 Ser Val Glu Asn Asp Ile His Gly Leu Arg Lys Val Ile Asp Asp Thr  
180 185 190  
40 Asn Ile Thr Arg Leu Gln Leu Glu Thr Glu Ile Glu Ala Leu Lys Glu  
195 200 205  
Glu Leu Leu Phe Met Lys Lys Asn His Glu Glu Glu Val Lys Gly Leu  
45 210 215 220  
Gln Ala Gln Ile Ala Ser Ser Gly Leu Thr Val Glu Val Asp Ala Pro  
225 230 235 240  
50 Lys Ser Gln Asp Leu Ala Lys Ile Met Ala Asp Ile Arg Ala Gln Tyr  
245 250 255  
55 Asp Glu Leu Ala Arg Lys Asn Arg Glu Glu Leu Asp Lys Tyr Trp Ser

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	260	265	270
5	Gln Gln Ile Glu Glu Ser Thr Thr Val Val Thr Thr Gln Ser Ala Glu		
	275	280	285
	Val Gly Ala Ala Glu Thr Thr Leu Thr Glu Leu Arg Arg Thr Val Gln		
10	290	295	300
	Ser Leu Glu Ile Asp Leu Asp Ser Met Arg Asn Leu Lys Ala Ser Leu		
	305	310	315
15	Glu Asn Ser Leu Arg Glu Val Glu Ala Arg Tyr Ala Leu Gln Met Glu		
	325	330	335
20	Gln Leu Asn Gly Ile Leu Leu His Leu Glu Ser Glu Leu Ala Gln Thr		
	340	345	350
	Arg Ala Glu Gly Gln Arg Gln Ala Gln Glu Tyr Glu Ala Leu Leu Asn		
25	355	360	365
	Ile Lys Val Lys Leu Glu Ala Glu Ile Ala Thr Tyr Arg Arg Leu Leu		
	370	375	380
30	Glu Asp Gly Glu Asp Phe Asn Leu Gly Asp Ala Leu Asp Ser Ser Asn		
	385	390	395
	Ser Met Gln Thr Ile Gln Lys Thr Thr Thr Arg Arg Ile Val Asp Gly		
35	405	410	415
	Lys Val Val Ser Glu Thr Asn Asp Thr Lys Val Leu Arg His		
40	420	425	430
45	<210> 118		
	<211> 400		
50	<212> PRT		
	<213> Homo sapiens		
55	<400> 118		



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Met Thr Ser Tyr Ser Tyr Arg Gln Ser Ser Ala Thr Ser Ser Phe Gly  
1 5 10 15  
5 Gly Leu Gly Gly Gly Ser Val Arg Phe Gly Pro Gly Val Ala Phe Arg  
20 25 30  
10 Ala Pro Ser Ile His Gly Gly Ser Gly Gly Arg Gly Val Ser Val Ser  
35 40 45  
Ser Ala Arg Phe Val Ser Ser Ser Ser Ser Gly Ala Tyr Gly Gly Gly  
15 50 55 60  
Tyr Gly Gly Val Leu Thr Ala Ser Asp Gly Leu Leu Ala Gly Asn Glu  
65 70 75 80  
20 Lys Leu Thr Met Gln Asn Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp  
85 90 95  
25 Lys Val Arg Ala Leu Glu Ala Ala Asn Gly Glu Leu Glu Val Lys Ile  
100 105 110  
Arg Asp Trp Tyr Gln Lys Gln Gly Pro Gly Pro Ser Arg Asp Tyr Ser  
30 115 120 125  
His Tyr Tyr Thr Thr Ile Gln Asp Leu Arg Asp Lys Ile Leu Gly Ala  
130 135 140  
35 Thr Ile Glu Asn Ser Arg Ile Val Leu Gln Ile Asp Asn Ala Arg Leu  
145 150 155 160  
40 Ala Ala Asp Asp Phe Arg Thr Lys Phe Glu Thr Glu Gln Ala Leu Arg  
165 170 175  
Met Ser Val Glu Ala Asp Ile Asn Gly Leu Arg Arg Val Leu Asp Glu  
45 180 185 190  
Leu Thr Leu Ala Arg Thr Asp Leu Glu Met Gln Ile Glu Gly Leu Lys  
195 200 205  
50 Glu Glu Leu Ala Tyr Leu Lys Lys Asn His Glu Glu Glu Ile Ser Thr  
210 215 220  
55 Leu Arg Gly Gln Val Gly Gly Gln Val Ser Val Glu Val Asp Ser Ala

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	225	230	235	240
5	Pro Gly Thr Asp Leu Ala Lys Ile Leu Ser Asp Met Arg Ser Gln Tyr			
		245	250	255
	Glu Val Met Ala Glu Gln Asn Arg Lys Asp Ala Glu Ala Trp Phe Thr			
10		260	265	270
	Ser Arg Thr Glu Glu Leu Asn Arg Glu Val Ala Gly His Thr Glu Gln			
		275	280	285
15	Leu Gln Met Ser Arg Ser Glu Val Thr Asp Leu Arg Arg Thr Leu Gln			
		290	295	300
20	Gly Leu Glu Ile Glu Leu Gln Ser Gln Leu Ser Met Lys Ala Ala Leu			
		305	310	315
	Glu Asp Thr Leu Ala Glu Thr Glu Ala Arg Phe Gly Ala Gln Leu Ala			
25		325	330	335
	His Ile Gln Ala Leu Ile Ser Gly Ile Glu Ala Gln Leu Gly Asp Val			
		340	345	350
30	Arg Ala Asp Ser Glu Arg Gln Asn Gln Glu Tyr Gln Arg Leu Met Asp			
		355	360	365
35	Ile Lys Ser Arg Leu Glu Gln Glu Ile Ala Thr Tyr Arg Ser Leu Leu			
		370	375	380
	Glu Gly Gln Glu Asp His Tyr Asn Asn Leu Ser Ala Ser Lys Val Leu			
40		385	390	395
				400
45	<210> 119			
	<211> 424			
	<212> PRT			
50	<213> Homo sapiens			
55	<400> 119			

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Met Asp Phe Ser Arg Arg Ser Phe His Arg Ser Leu Ser Ser Ser Leu  
1 5 10 15  
5 Gln Ala Pro Val Val Ser Thr Val Gly Met Gln Arg Leu Gly Thr Thr  
20 25 30  
10 Pro Ser Val Tyr Gly Gly Ala Gly Gly Arg Gly Ile Arg Ile Ser Asn  
35 40 45  
Ser Arg His Thr Val Asn Tyr Gly Ser Asp Leu Thr Gly Gly Gly Asp  
15 50 55 60  
Leu Phe Val Gly Asn Glu Lys Met Ala Met Gln Asn Leu Asn Asp Arg  
65 70 75 80  
20 Leu Ala Ser Tyr Leu Glu Lys Val Arg Thr Leu Glu Gln Ser Asn Ser  
85 90 95  
25 Lys Leu Glu Val Gln Ile Lys Gln Trp Tyr Glu Thr Asn Ala Pro Arg  
100 105 110  
Ala Gly Arg Asp Tyr Ser Ala Tyr Tyr Arg Gln Ile Glu Glu Leu Arg  
30 115 120 125  
Ser Gln Ile Lys Asp Ala Gln Leu Gln Asn Ala Arg Cys Val Leu Gln  
130 135 140  
35 Ile Asp Asn Ala Lys Leu Ala Ala Glu Asp Phe Arg Leu Lys Tyr Glu  
145 150 155 160  
40 Thr Glu Arg Gly Ile Arg Leu Thr Val Glu Ala Asp Leu Gln Gly Leu  
165 170 175  
Asn Lys Val Phe Asp Asp Leu Thr Leu His Lys Thr Asp Leu Glu Ile  
45 180 185 190  
Gln Ile Glu Glu Leu Asn Lys Asp Leu Ala Leu Leu Lys Lys Glu His  
195 200 205  
50 Gln Glu Glu Val Asp Gly Leu His Lys His Leu Gly Asn Thr Val Asn  
210 215 220  
Val Glu Val Asp Ala Ala Pro Gly Leu Asn Leu Gly Val Ile Met Asn  
55

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225                      230                      235                      240  
 5      Glu Met Arg Gln Lys Tyr Glu Val Met Ala Gln Lys Asn Leu Gln Glu  
                          245                      250                      255  
     Ala Lys Glu Gln Phe Glu Arg Gln Thr Ala Val Leu Gln Gln Gln Val  
 10                      260                      265                      270  
     Thr Val Asn Thr Glu Glu Leu Lys Gly Thr Glu Val Gln Leu Thr Glu  
                          275                      280                      285  
 15      Leu Arg Arg Thr Ser Gln Ser Leu Glu Ile Glu Leu Gln Ser His Leu  
                          290                      295                      300  
     Ser Met Lys Glu Ser Leu Glu His Thr Leu Glu Glu Thr Lys Ala Arg  
 20      305                      310                      315                      320  
     Tyr Ser Ser Gln Leu Ala Asn Leu Gln Ser Leu Leu Ser Ser Leu Glu  
                          325                      330                      335  
 25      Ala Gln Leu Met Gln Ile Arg Ser Asn Met Glu Arg Gln Asn Asn Glu  
                          340                      345                      350  
 30      Tyr His Ile Leu Leu Asp Ile Lys Thr Arg Leu Glu Gln Glu Ile Ala  
                          355                      360                      365  
     Thr Tyr Arg Arg Leu Leu Glu Gly Glu Asp Val Lys Thr Thr Glu Tyr  
 35      370                      375                      380  
     Gln Leu Ser Thr Leu Glu Glu Arg Asp Ile Lys Lys Thr Arg Lys Ile  
 40      385                      390                      395                      400  
     Lys Thr Val Val Gln Glu Val Val Asp Gly Lys Val Val Ser Ser Glu  
                          405                      410                      415  
 45      Val Lys Glu Val Glu Glu Asn Ile  
                          420

<210> 120

<211> 1255

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<212> PRT

5 <213> Homo sapiens

<400> 120

10 Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr  
1 5 10 15  
15 Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30  
Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
20 35 40 45  
Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His  
50 55 60  
25 Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu  
65 70 75 80  
Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln  
30 85 90 95  
Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr  
35 100 105 110  
Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro  
115 120 125  
40 Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
130 135 140  
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
45 145 150 155 160  
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
50 165 170 175  
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
180 185 190  
55 Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro

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	195	200	205
5	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
	210	215	220
	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
10	225	230	235
	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
	245	250	255
15	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
	260	265	270
20	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
	275	280	285
	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
25	290	295	300
	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
	305	310	315
30	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
	325	330	335
35	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
	340	345	350
	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
40	355	360	365
	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
	370	375	380
45	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
	385	390	395
	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
50	405	410	415
	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
55	420	425	430

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Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
5 435 440 445  
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
450 455 460  
10 Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
465 470 475 480  
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
15 485 490 495  
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
500 505 510  
20 Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
515 520 525  
25 Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
530 535 540  
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
30 545 550 555 560  
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
565 570 575  
35 Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
580 585 590  
40 Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
595 600 605  
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
45 610 615 620  
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
625 630 635 640  
50 Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
645 650 655  
55 Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala

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	660	665	670
5	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
	675	680	685
	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
10	690	695	700
	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
	705	710	715
15	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
	725	730	735
	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
20	740	745	750
	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
25	755	760	765
	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
	770	775	780
30	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
	785	790	795
	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
35	805	810	815
	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
40	820	825	830
	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
	835	840	845
45	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
	850	855	860
	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
50	865	870	875
	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
55	885	890	895



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Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
 900 905 910  
 5 Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
 915 920 925  
 10 Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn  
 930 935 940  
 Arg Pro Ala Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser  
 15 945 950 955 960  
 Ala Ser Gly Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly  
 965 970 975  
 20 Thr Ser Ala Arg Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe  
 980 985 990  
 25 Ser Ile Pro Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His  
 995 1000 1005  
 Ser Thr Lys Thr Asp Ala Ser Ser Thr His His Ser Ser Val Pro Pro  
 30 1010 1015 1020  
 Leu Thr Ser Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val  
 1025 1030 1035 1040  
 35 Ser Phe Phe Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser  
 1045 1050 1055  
 40 Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp  
 1060 1065 1070  
 Ile Ser Glu Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly  
 45 1075 1080 1085  
 Leu Ser Asn Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr  
 1090 1095 1100  
 50 Leu Ala Phe Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln  
 1105 1110 1115 1120  
 55 Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile

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1125 1130 1135  
 5 Ser Asp Val Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser  
 1140 1145 1150  
 Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys  
 10 1155 1160 1165  
 Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys  
 1170 1175 1180  
 15 Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg  
 1185 1190 1195 1200  
 Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly  
 20 1205 1210 1215  
 Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val  
 25 1220 1225 1230  
 Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val  
 1235 1240 1245  
 30 Ala Ala Ala Ser Ala Asn Leu  
 1250 1255  
 35  
 <210> 121  
 40 <211> 5179  
 <212> PRT  
 <213> Homo sapiens  
 45  
 <400> 121  
 Met Gly Leu Pro Leu Ala Arg Leu Ala Ala Val Cys Leu Ala Leu Ser  
 50 1 5 10 15  
 Leu Ala Gly Gly Ser Glu Leu Gln Thr Glu Gly Arg Thr Arg Tyr His  
 55 20 25 30

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	Gly	Arg	Asn	Val	Cys	Ser	Thr	Trp	Gly	Asn	Phe	His	Tyr	Lys	Thr	Phe	
5				35					40					45			
	Asp	Gly	Asp	Val	Phe	Arg	Phe	Pro	Gly	Leu	Cys	Asp	Tyr	Asn	Phe	Ala	
		50					55					60					
10	Ser	Asp	Cys	Arg	Gly	Ser	Tyr	Lys	Glu	Phe	Ala	Val	His	Leu	Lys	Arg	
	65					70					75					80	
	Gly	Pro	Gly	Gln	Ala	Glu	Ala	Pro	Ala	Gly	Val	Glu	Ser	Ile	Leu	Leu	
15					85					90					95		
	Thr	Ile	Lys	Asp	Asp	Thr	Ile	Tyr	Leu	Thr	Arg	His	Leu	Ala	Val	Leu	
			100						105					110			
20	Asn	Gly	Ala	Val	Val	Ser	Thr	Pro	His	Tyr	Ser	Pro	Gly	Leu	Leu	Ile	
		115					120					125					
25	Glu	Lys	Ser	Asp	Ala	Tyr	Thr	Lys	Val	Tyr	Ser	Arg	Ala	Gly	Leu	Thr	
		130				135					140						
	Leu	Met	Trp	Asn	Arg	Glu	Asp	Ala	Leu	Met	Leu	Glu	Leu	Asp	Thr	Lys	
30	145				150					155						160	
	Phe	Arg	Asn	His	Thr	Cys	Gly	Leu	Cys	Gly	Asp	Tyr	Asn	Gly	Leu	Gln	
				165					170						175		
35	Ser	Tyr	Ser	Glu	Phe	Leu	Ser	Asp	Gly	Val	Leu	Phe	Ser	Pro	Leu	Glu	
			180						185				190				
40	Phe	Gly	Asn	Met	Gln	Lys	Ile	Asn	Gln	Pro	Asp	Val	Val	Cys	Glu	Asp	
		195					200					205					
	Pro	Glu	Glu	Glu	Val	Ala	Pro	Ala	Ser	Cys	Ser	Glu	His	Arg	Ala	Glu	
45		210				215					220						
	Cys	Glu	Arg	Leu	Leu	Thr	Ala	Glu	Ala	Phe	Ala	Asp	Cys	Gln	Asp	Leu	
	225				230					235						240	
50	Val	Pro	Leu	Glu	Pro	Tyr	Leu	Arg	Ala	Cys	Gln	Gln	Asp	Arg	Cys	Arg	
				245					250						255		
55	Cys	Pro	Gly	Gly	Asp	Thr	Cys	Val	Cys	Ser	Thr	Val	Ala	Glu	Phe	Ser	

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	260	265	270
5	Arg Gln Cys Ser His Ala Gly Gly Arg Pro Gly Asn Trp Arg Thr Ala		
	275	280	285
	Thr Leu Cys Pro Lys Thr Cys Pro Gly Asn Leu Val Tyr Leu Glu Ser		
10	290	295	300
	Gly Ser Pro Cys Met Asp Thr Cys Ser His Leu Glu Val Ser Ser Leu		
	305	310	315
15	Cys Glu Glu His Arg Met Asp Gly Cys Phe Cys Pro Glu Gly Thr Val		
	325	330	335
20	Tyr Asp Asp Ile Gly Asp Ser Gly Cys Val Pro Val Ser Gln Cys His		
	340	345	350
	Cys Arg Leu His Gly His Leu Tyr Thr Pro Gly Gln Glu Ile Thr Asn		
25	355	360	365
	Asp Cys Glu Gln Cys Val Cys Asn Ala Gly Arg Trp Val Cys Lys Asp		
	370	375	380
30	Leu Pro Cys Pro Gly Thr Cys Ala Leu Glu Gly Gly Ser His Ile Thr		
	385	390	395
	Thr Phe Asp Gly Lys Thr Tyr Thr Phe His Gly Asp Cys Tyr Tyr Val		
35	405	410	415
	Leu Ala Lys Gly Asp His Asn Asp Ser Tyr Ala Leu Leu Gly Glu Leu		
40	420	425	430
	Ala Pro Cys Gly Ser Thr Asp Lys Gln Thr Cys Leu Lys Thr Val Val		
	435	440	445
45	Leu Leu Ala Asp Lys Lys Lys Asn Ala Val Val Phe Lys Ser Asp Gly		
	450	455	460
	Ser Val Leu Leu Asn Gln Leu Gln Val Asn Leu Pro His Val Thr Ala		
50	465	470	475
	Ser Phe Ser Val Phe Arg Pro Ser Ser Tyr His Ile Met Val Ser Met		
	485	490	495
55			

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Ala Ile Gly Val Arg Leu Gln Val Gln Leu Ala Pro Val Met Gln Leu  
5 500 505 510  
Phe Val Thr Leu Asp Gln Ala Ser Gln Gly Gln Val Gln Gly Leu Cys  
515 520 525  
10 Gly Asn Phe Asn Gly Leu Glu Gly Asp Asp Phe Lys Thr Ala Ser Gly  
530 535 540  
Leu Val Glu Ala Thr Gly Ala Gly Phe Ala Asn Thr Trp Lys Ala Gln  
15 545 550 555 560  
Ser Thr Cys His Asp Lys Leu Asp Trp Leu Asp Asp Pro Cys Ser Leu  
565 570 575  
20 Asn Ile Glu Ser Ala Asn Tyr Ala Glu His Trp Cys Ser Leu Leu Lys  
580 585 590  
25 Lys Thr Glu Thr Pro Phe Gly Arg Cys His Ser Ala Val Asp Pro Ala  
595 600 605  
Glu Tyr Tyr Lys Arg Cys Lys Tyr Asp Thr Cys Asn Cys Gln Asn Asn  
30 610 615 620  
Glu Asp Cys Leu Cys Ala Ala Leu Ser Ser Tyr Ala Arg Ala Cys Thr  
625 630 635 640  
35 Ala Lys Gly Val Met Leu Trp Gly Trp Arg Glu His Val Cys Asn Lys  
645 650 655  
40 Asp Val Gly Ser Cys Pro Asn Ser Gln Val Phe Leu Tyr Asn Leu Thr  
660 665 670  
Thr Cys Gln Gln Thr Cys Arg Ser Leu Ser Glu Ala Asp Ser His Cys  
45 675 680 685  
Leu Glu Gly Phe Ala Pro Val Asp Gly Cys Gly Cys Pro Asp His Thr  
690 695 700  
50 Phe Leu Asp Glu Lys Gly Arg Cys Val Pro Leu Ala Lys Cys Ser Cys  
705 710 715 720  
55 Tyr His Arg Gly Leu Tyr Leu Glu Ala Gly Asp Val Val Val Arg Gln

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	725	730	735
5	Glu Glu Arg Cys Val Cys Arg Asp Gly Arg Leu His Cys Arg Gln Ile		
	740	745	750
	Arg Leu Ile Gly Gln Ser Cys Thr Ala Pro Lys Ile His Met Asp Cys		
10	755	760	765
	Ser Asn Leu Thr Ala Leu Ala Thr Ser Lys Pro Arg Ala Leu Ser Cys		
	770	775	780
15	Gln Thr Leu Ala Ala Gly Tyr Tyr His Thr Glu Cys Val Ser Gly Cys		
	785	790	795 800
20	Val Cys Pro Asp Gly Leu Met Asp Asp Gly Arg Gly Gly Cys Val Val		
	805	810	815
	Glu Lys Glu Cys Pro Cys Val His Asn Asn Asp Leu Tyr Ser Ser Gly		
25	820	825	830
	Ala Lys Ile Lys Val Asp Cys Asn Thr Cys Thr Cys Lys Arg Gly Arg		
	835	840	845
30	Trp Val Cys Thr Gln Ala Val Cys His Gly Thr Cys Ser Ile Tyr Gly		
	850	855	860
	Ser Gly His Tyr Ile Thr Phe Asp Gly Lys Tyr Tyr Asp Phe Asp Gly		
35	865	870	875 880
	His Cys Ser Tyr Val Ala Val Gln Asp Tyr Cys Gly Gln Asn Ser Ser		
40	885	890	895
	Leu Gly Ser Phe Ser Ile Ile Thr Glu Asn Val Pro Cys Gly Thr Thr		
	900	905	910
45	Gly Val Thr Cys Ser Lys Ala Ile Lys Ile Phe Met Gly Arg Thr Glu		
	915	920	925
	Leu Lys Leu Glu Asp Lys His Arg Val Val Ile Gln Arg Asp Glu Gly		
50	930	935	940
	His His Val Ala Tyr Thr Thr Arg Glu Val Gly Gln Tyr Leu Val Val		
55	945	950	955 960

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Glu Ser Ser Thr Gly Ile Ile Val Ile Trp Asp Lys Arg Thr Thr Val  
 5                           965                           970                           975  
 Phe Ile Lys Leu Ala Pro Ser Tyr Lys Gly Thr Val Cys Gly Leu Cys  
 980                           985                           990  
 10 Gly Asn Phe Asp His Arg Ser Asn Asn Asp Phe Thr Thr Arg Asp His  
 995                           1000                           1005  
 Met Val Val Ser Ser Glu Leu Asp Phe Gly Asn Ser Trp Lys Glu Ala  
 15           1010                           1015                           1020  
 Pro Thr Cys Pro Asp Val Ser Thr Asn Pro Glu Pro Cys Ser Leu Asn  
 1025                           1030                           1035                           1040  
 20 Pro His Arg Arg Ser Trp Ala Glu Lys Gln Cys Ser Ile Leu Lys Ser  
 1045                           1050                           1055  
 25 Ser Val Phe Ser Ile Cys His Ser Lys Val Asp Pro Lys Pro Phe Tyr  
 1060                           1065                           1070  
 Glu Ala Cys Val His Asp Ser Cys Ser Cys Asp Thr Gly Gly Asp Cys  
 30           1075                           1080                           1085  
 Glu Cys Phe Cys Ser Ala Val Ala Ser Tyr Ala Gln Glu Cys Thr Lys  
 1090                           1095                           1100  
 35 Glu Gly Ala Cys Val Phe Trp Arg Thr Pro Asp Leu Cys Pro Ile Phe  
 1105                           1110                           1115                           1120  
 40 Cys Asp Tyr Tyr Asn Pro Pro His Glu Cys Glu Trp His Tyr Glu Pro  
 1125                           1130                           1135  
 Cys Gly Asn Arg Ser Phe Glu Thr Cys Arg Thr Ile Asn Gly Ile His  
 45           1140                           1145                           1150  
 Ser Asn Ile Ser Val Ser Tyr Leu Glu Gly Cys Tyr Pro Arg Cys Pro  
 1155                           1160                           1165  
 50 Lys Asp Arg Pro Ile Tyr Glu Glu Asp Leu Lys Lys Cys Val Thr Ala  
 1170                           1175                           1180  
 55 Asp Lys Cys Gly Cys Tyr Val Glu Asp Thr His Tyr Pro Pro Gly Ala

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	1185	1190	1195	1200
5	Ser Val Pro Thr Glu Glu Thr Cys Lys Ser Cys Val Cys Thr Asn Ser			
	1205	1210	1215	
	Ser Gln Val Val Cys Arg Pro Glu Glu Gly Lys Ile Leu Asn Gln Thr			
10	1220	1225	1230	
	Gln Asp Gly Ala Phe Cys Tyr Trp Glu Ile Cys Gly Pro Asn Gly Thr			
	1235	1240	1245	
15	Val Glu Lys His Phe Asn Ile Cys Ser Ile Thr Thr Arg Pro Ser Thr			
	1250	1255	1260	
	Leu Thr Thr Phe Thr Thr Ile Thr Leu Pro Thr Thr Pro Thr Ser Phe			
20	1265	1270	1275	1280
	Thr Thr Thr Thr Thr Thr Thr Thr Pro Thr Ser Ser Thr Val Leu Ser			
25	1285	1290	1295	
	Thr Thr Pro Lys Leu Cys Cys Leu Trp Ser Asp Trp Ile Asn Glu Asp			
	1300	1305	1310	
30	His Pro Ser Ser Gly Ser Asp Asp Gly Asp Arg Glu Pro Phe Asp Gly			
	1315	1320	1325	
	Val Cys Gly Ala Pro Glu Asp Ile Glu Cys Arg Ser Val Lys Asp Pro			
35	1330	1335	1340	
	His Leu Ser Leu Glu Gln His Gly Gln Lys Val Gln Cys Asp Val Ser			
40	1345	1350	1355	1360
	Val Gly Phe Ile Cys Lys Asn Glu Asp Gln Phe Gly Asn Gly Pro Phe			
	1365	1370	1375	
45	Gly Leu Cys Tyr Asp Tyr Lys Ile Arg Val Asn Cys Cys Trp Pro Met			
	1380	1385	1390	
	Asp Lys Cys Ile Thr Thr Pro Ser Pro Pro Thr Thr Thr Pro Ser Pro			
50	1395	1400	1405	
	Pro Pro Thr Thr Thr Thr Thr Leu Pro Pro Thr Thr Thr Pro Ser Pro			
55	1410	1415	1420	



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Pro Thr Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro  
1425 1430 1435 1440  
5 Pro Ile Thr Thr Thr Thr Thr Pro Leu Pro Thr Thr Thr Pro Ser Pro  
1445 1450 1455  
10 Pro Ile Ser Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro  
1460 1465 1470  
Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr Pro Ser Pro Pro Thr  
15 1475 1480 1485  
Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro Pro Met  
1490 1495 1500  
20 Thr Thr Pro Ile Thr Pro Pro Ala Ser Thr Thr Thr Leu Pro Pro Thr  
1505 1510 1515 1520  
25 Thr Thr Pro Ser Pro Pro Thr Thr Thr Thr Thr Pro Pro Pro Thr  
1525 1530 1535  
Thr Thr Pro Ser Pro Pro Thr Thr Thr Pro Ile Thr Pro Pro Thr Ser  
30 1540 1545 1550  
Thr Thr Thr Leu Pro Pro Thr Thr Thr Pro Ser Pro Pro Pro Thr Thr  
1555 1560 1565  
35 Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr  
1570 1575 1580  
40 Thr Pro Ser Pro Pro Thr Ile Thr Thr Thr Thr Pro Pro Pro Thr Thr  
1585 1590 1595 1600  
Thr Pro Ser Pro Pro Thr Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr  
45 1605 1610 1615  
Thr Pro Ser Pro Pro Thr Thr Thr Pro Ile Thr Pro Pro Thr Ser Thr  
1620 1625 1630  
50 Thr Thr Leu Pro Pro Thr Thr Thr Pro Ser Pro Pro Pro Thr Thr Thr  
1635 1640 1645  
55 Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr Thr

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	1650	1655	1660
5	Pro Ser Pro Pro Ile Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr		
	1665	1670	1675 1680
	Pro Ser Ser Pro Ile Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr Met		
10	1685	1690	1695
	Thr Thr Pro Ser Pro Thr Thr Thr Pro Ser Ser Pro Ile Thr Thr Thr		
	1700	1705	1710
15	Thr Thr Pro Ser Ser Thr Thr Thr Pro Ser Pro Pro Pro Thr Thr Met		
	1715	1720	1725
20	Thr Thr Pro Ser Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr Met		
	1730	1735	1740
	Thr Thr Leu Pro Pro Thr Thr Thr Ser Ser Pro Leu Thr Thr Thr Pro		
25	1745	1750	1755 1760
	Leu Pro Pro Ser Ile Thr Pro Pro Thr Phe Ser Pro Phe Ser Thr Thr		
	1765	1770	1775
30	Thr Pro Thr Thr Pro Cys Val Pro Leu Cys Asn Trp Thr Gly Trp Leu		
	1780	1785	1790
	Asp Ser Gly Lys Pro Asn Phe His Lys Pro Gly Gly Asp Thr Glu Leu		
35	1795	1800	1805
	Ile Gly Asp Val Cys Gly Pro Gly Trp Ala Ala Asn Ile Ser Cys Arg		
40	1810	1815	1820
	Ala Thr Met Tyr Pro Asp Val Pro Ile Gly Gln Leu Gly Gln Thr Val		
	1825	1830	1835 1840
45	Val Cys Asp Val Ser Val Gly Leu Ile Cys Lys Asn Glu Asp Gln Lys		
	1845	1850	1855
	Pro Gly Gly Val Ile Pro Met Ala Phe Cys Leu Asn Tyr Glu Ile Asn		
50	1860	1865	1870
	Val Gln Cys Cys Glu Cys Val Thr Gln Pro Thr Thr Met Thr Thr Thr		
55	1875	1880	1885

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Thr Thr Glu Asn Pro Thr Pro Pro Thr Thr Thr Pro Ile Thr Thr Thr  
 5                   1890                   1895                   1900  
 Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr  
 1905                   1910                   1915                   1920  
 10   ; Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro  
                   1925                   1930                   1935  
 Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr  
 15                   1940                   1945                   1950  
 Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr  
 20   )                   1955                   1960                   1965  
 Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly  
                   1970                   1975                   1980  
 25 Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr  
 1985                   1990                   1995                   2000  
 ; Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile  
 30                   2005                   2010                   2015  
 Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln  
                   2020                   2025                   2030  
 35 Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr  
 ;                   2035                   2040                   2045  
 40 Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr  
                   2050                   2055                   2060  
 Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro  
 45 2065                   2070                   2075                   2080  
 ; Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr  
                   2085                   2090                   2095  
 50 Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr  
                   2100                   2105                   2110  
 55 Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr

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	2115	2120	2125
5	Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr		
	2130	2135	2140
	Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val		
10	2145	2150	2155
	Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro		
	2165	2170	2175
15	Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr		
	2180	2185	2190
20	Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro		
	2195	2200	2205
	Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr		
25	2210	2215	2220
	Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr		
	2225	2230	2235
30	Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro		
	2245	2250	2255
35	Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr		
	2260	2265	2270
	Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr		
40	2275	2280	2285
	Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro		
	2290	2295	2300
45	Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr		
	2305	2310	2315
	Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr		
50	2325	2330	2335
	Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly		
55	2340	2345	2350

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Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr  
5 2355 2360 2365  
Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile  
2370 2375 2380  
10 Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln  
2385 2390 2395 2400  
Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr  
15 2405 2410 2415  
Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr  
2420 2425 2430  
20 Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro  
2435 2440 2445  
25 Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr  
2450 2455 2460  
Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr  
30 2465 2470 2475 2480  
Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr  
2485 2490 2495  
35 Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr  
2500 2505 2510  
40 Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val  
2515 2520 2525  
Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro  
45 2530 2535 2540  
Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr  
2545 2550 2555 2560  
50 Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro  
2565 2570 2575  
55 Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr

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	2580	2585	2590
5	Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr		
	2595	2600	2605
	Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro		
10	2610	2615	2620
	Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr		
	2625	2630	2635
15	2640		
	Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr		
	2645	2650	2655
20	2660	2665	2670
	Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro		
	Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr		
25	2675	2680	2685
	Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr		
	2690	2695	2700
30	2705	2710	2715
	Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly		
	Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr		
35	2725	2730	2735
	Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile		
40	2740	2745	2750
	Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln		
	2755	2760	2765
45	2770	2775	2780
	Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr		
	Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr		
50	2785	2790	2795
	Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro		
55	2805	2810	2815

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Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr  
5 2820 2825 2830  
Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr  
2835 2840 2845  
10 Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr  
2850 2855 2860  
Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr  
15 2865 2870 2875 2880  
Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val  
2885 2890 2895  
20 Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro  
2900 2905 2910  
25 Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr  
2915 2920 2925  
Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro  
30 2930 2935 2940  
Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr  
2945 2950 2955 2960  
35 Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr  
2965 2970 2975  
40 Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro  
2980 2985 2990  
Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr  
45 2995 3000 3005  
Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr  
3010 3015 3020  
50 Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro  
3025 3030 3035 3040  
55 Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr

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	3045	3050	3055
5	Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr		
	3060	3065	3070
	Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly		
10	3075	3080	3085
	Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr		
	3090	3095	3100
15	Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile		
	3105	3110	3115
	3120		
	Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln		
20	3125	3130	3135
	Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr		
25	3140	3145	3150
	Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr		
	3155	3160	3165
30	Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro		
	3170	3175	3180
	Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr		
35	3185	3190	3195
	3200		
	Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr		
40	3205	3210	3215
	Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr		
	3220	3225	3230
45	Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr		
	3235	3240	3245
	Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val		
50	3250	3255	3260
	Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro		
55	3265	3270	3275
	3280		



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Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr  
5 3285 3290 3295  
Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro  
3300 3305 3310  
10 Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr  
3315 3320 3325  
Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr  
15 3330 3335 3340  
Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro  
20 3345 3350 3355 3360  
Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr  
3365 3370 3375  
25 Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr  
3380 3385 3390  
Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro  
30 3395 3400 3405  
Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr  
3410 3415 3420  
35 Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr  
3425 3430 3435 3440  
40 Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly  
3445 3450 3455  
Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr  
45 3460 3465 3470  
Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile  
3475 3480 3485  
50 Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln  
3490 3495 3500  
55 Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr

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	3505	3510	3515	3520
5	Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr			
		3525	3530	3535
	Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro			
10		3540	3545	3550
	Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr			
		3555	3560	3565
15	Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr			
		3570	3575	3580
	Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr			
20		3585	3590	3595
				3600
	Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr			
25		3605	3610	3615
	Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val			
		3620	3625	3630
30	Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro			
		3635	3640	3645
	Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr			
35		3650	3655	3660
	Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro			
40		3665	3670	3675
				3680
	Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr			
		3685	3690	3695
45	Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr			
		3700	3705	3710
	Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro			
50		3715	3720	3725
	Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr			
55		3730	3735	3740

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Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr  
5 3745 3750 3755 3760  
Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro  
3765 3770 3775  
10 Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr  
3780 3785 3790  
Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr  
15 3795 3800 3805  
Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly  
20 3810 3815 3820  
Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr  
3825 3830 3835 3840  
25 Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile  
3845 3850 3855  
Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln  
30 3860 3865 3870  
Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr  
3875 3880 3885  
35 Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr  
3890 3895 3900  
40 Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro  
3905 3910 3915 3920  
Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr  
45 3925 3930 3935  
Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr  
3940 3945 3950  
50 Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr  
3955 3960 3965  
55 Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr

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	3970	3975	3980	
5	Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val			
	3985	3990	3995	4000
	Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro			
10		4005	4010	4015
	Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr			
		4020	4025	4030
15	Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro			
		4035	4040	4045
	Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr			
20		4050	4055	4060
	Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr			
25	4065	4070	4075	4080
	Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro			
		4085	4090	4095
30	Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr			
		4100	4105	4110
	Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr			
35		4115	4120	4125
	Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro			
40	4130	4135	4140	
	Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr			
	4145	4150	4155	4160
45	Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr			
		4165	4170	4175
	Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly			
50		4180	4185	4190
	Thr Gln Thr Gly Pro Pro Thr His Thr Ser Thr Ala Pro Ile Ala Glu			
55		4195	4200	4205

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Leu Thr Thr Ser Asn Pro Pro Pro Glu Ser Ser Thr Pro Gln Thr Ser  
 5           4210                   4215                   4220  
 Arg Ser Thr Ser Ser Pro Leu Thr Glu Ser Thr Thr Leu Leu Ser Thr  
 4225                   4230                   4235                   4240  
 10 Leu Pro Pro Ala Ile Glu Met Thr Ser Thr Ala Pro Pro Ser Thr Pro  
                  4245                   4250                   4255  
 Thr Ala Pro Thr Thr Thr Ser Gly Gly His Thr Leu Ser Pro Pro Pro  
 15                   4260                   4265                   4270  
 Ser Thr Thr Thr Ser Pro Pro Gly Thr Pro Thr Arg Gly Thr Thr Thr  
 20                   4275                   4280                   4285  
 Gly Ser Ser Ser Ala Pro Thr Pro Ser Thr Val Gln Thr Thr Thr Thr  
                  4290                   4295                   4300  
 25 Ser Ala Trp Thr Pro Thr Pro Thr Pro Leu Ser Thr Pro Ser Ile Ile  
 4305                   4310                   4315                   4320  
 Arg Thr Thr Gly Leu Arg Pro Tyr Pro Ser Ser Val Leu Ile Cys Cys  
 30                   4325                   4330                   4335  
 Val Leu Asn Asp Thr Tyr Tyr Ala Pro Gly Glu Glu Val Tyr Asn Gly  
                  4340                   4345                   4350  
 35 Thr Tyr Gly Asp Thr Cys Tyr Phe Val Asn Cys Ser Leu Ser Cys Thr  
                  4355                   4360                   4365  
 40 Leu Glu Phe Tyr Asn Trp Ser Cys Pro Ser Thr Pro Ser Pro Thr Pro  
                  4370                   4375                   4380  
 Thr Pro Ser Lys Ser Thr Pro Thr Pro Ser Lys Pro Ser Ser Thr Pro  
 45 4385                   4390                   4395                   4400  
 Ser Lys Pro Thr Pro Gly Thr Lys Pro Pro Glu Cys Pro Asp Phe Asp  
                  4405                   4410                   4415  
 50 Pro Pro Arg Gln Glu Asn Glu Thr Trp Trp Leu Cys Asp Cys Phe Met  
                  4420                   4425                   4430  
 55 Ala Thr Cys Lys Tyr Asn Asn Thr Val Glu Ile Val Lys Val Glu Cys

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	4435	4440	4445
5	Glu Pro Pro Pro Met Pro Thr Cys Ser Asn Gly Leu Gln Pro Val Arg		
	4450	4455	4460
	Val Glu Asp Pro Asp Gly Cys Cys Trp His Trp Glu Cys Asp Cys Tyr		
10	4465	4470	4475
	Cys Thr Gly Trp Gly Asp Pro His Tyr Val Thr Phe Asp Gly Leu Tyr		
	4485	4490	4495
15	Tyr Ser Tyr Gln Gly Asn Cys Thr Tyr Val Leu Val Glu Glu Ile Ser		
	4500	4505	4510
20	Pro Ser Val Asp Asn Phe Gly Val Tyr Ile Asp Asn Tyr His Cys Asp		
	4515	4520	4525
	Pro Asn Asp Lys Val Ser Cys Pro Arg Thr Leu Ile Val Arg His Glu		
25	4530	4535	4540
	Thr Gln Glu Val Leu Ile Lys Thr Val His Met Met Pro Met Gln Val		
	4545	4550	4555
30	Gln Val Gln Val Asn Arg Gln Ala Val Ala Leu Pro Tyr Lys Lys Tyr		
	4565	4570	4575
35	Gly Leu Glu Val Tyr Gln Ser Gly Ile Asn Tyr Val Val Asp Ile Pro		
	4580	4585	4590
	Glu Leu Gly Val Leu Val Ser Tyr Asn Gly Leu Ser Phe Ser Val Arg		
40	4595	4600	4605
	Leu Pro Tyr His Arg Phe Gly Asn Asn Thr Lys Gly Gln Cys Gly Thr		
	4610	4615	4620
45	Cys Thr Asn Thr Thr Ser Asp Asp Cys Ile Leu Pro Ser Gly Glu Ile		
	4625	4630	4635
	Val Ser Asn Cys Glu Ala Ala Ala Asp Gln Trp Leu Val Asn Asp Pro		
50	4645	4650	4655
	Ser Lys Pro His Cys Pro His Ser Ser Ser Thr Thr Lys Arg Pro Ala		
55	4660	4665	4670

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Val Thr Val Pro Gly Gly Gly Lys Thr Thr Pro His Lys Asp Cys Thr  
5 4675 4680 4685  
Pro Ser Pro Leu Cys Gln Leu Ile Lys Asp Ser Leu Phe Ala Gln Cys  
4690 4695 4700  
10 His Ala Leu Val Pro Pro Gln His Tyr Tyr Asp Ala Cys Val Phe Asp  
4705 4710 4715 4720  
Ser Cys Phe Met Pro Gly Ser Ser Leu Glu Cys Ala Ser Leu Gln Ala  
15 4725 4730 4735  
Tyr Ala Ala Leu Cys Ala Gln Gln Asn Ile Cys Leu Asp Trp Arg Asn  
4740 4745 4750  
20 His Thr His Gly Ala Cys Leu Val Glu Cys Pro Ser His Arg Glu Tyr  
4755 4760 4765  
25 Gln Ala Cys Gly Pro Ala Glu Glu Pro Thr Cys Lys Ser Ser Ser Ser  
4770 4775 4780  
Gln Gln Asn Asn Thr Val Leu Val Glu Gly Cys Phe Cys Pro Glu Gly  
30 4785 4790 4795 4800  
Thr Met Asn Tyr Ala Pro Gly Phe Asp Val Cys Val Lys Thr Cys Gly  
4805 4810 4815  
35 Cys Val Gly Pro Asp Asn Val Pro Arg Glu Phe Gly Glu His Phe Glu  
4820 4825 4830  
40 Phe Asp Cys Lys Asn Cys Val Cys Leu Glu Gly Gly Ser Gly Ile Ile  
4835 4840 4845  
Cys Gln Pro Lys Arg Cys Ser Gln Lys Pro Val Thr His Cys Val Glu  
45 4850 4855 4860  
Asp Gly Thr Tyr Leu Ala Thr Glu Val Asn Pro Ala Asp Thr Cys Cys  
4865 4870 4875 4880  
50 Asn Ile Thr Val Cys Lys Cys Asn Thr Ser Leu Cys Lys Glu Lys Pro  
4885 4890 4895  
55 Ser Val Cys Pro Leu Gly Phe Glu Val Lys Ser Lys Met Val Pro Gly

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	4900	4905	4910	
5	Arg Cys Cys Pro Phe Tyr Trp Cys Glu Ser Lys Gly Val Cys Val His			
	4915	4920	4925	
	Gly Asn Ala Glu Tyr Gln Pro Gly Ser Pro Val Tyr Ser Ser Lys Cys			
10	4930	4935	4940	
	Gln Asp Cys Val Cys Thr Asp Lys Val Asp Asn Asn Thr Leu Leu Asn			
	4945	4950	4955	4960
15	Val Ile Ala Cys Thr His Val Pro Cys Asn Thr Ser Cys Ser Pro Gly			
	4965	4970	4975	
20	Phe Glu Leu Met Glu Ala Pro Gly Glu Cys Cys Lys Lys Cys Glu Gln			
	4980	4985	4990	
	Thr His Cys Ile Ile Lys Arg Pro Asp Asn Gln His Val Ile Leu Lys			
25	4995	5000	5005	
	Pro Gly Asp Phe Lys Ser Asp Pro Lys Asn Asn Cys Thr Phe Phe Ser			
	5010	5015	5020	
30	Cys Val Lys Ile His Asn Gln Leu Ile Ser Ser Val Ser Asn Ile Thr			
	5025	5030	5035	5040
35	Cys Pro Asn Phe Asp Ala Ser Ile Cys Ile Pro Gly Ser Ile Thr Phe			
	5045	5050	5055	
	Met Pro Asn Gly Cys Cys Lys Thr Cys Thr Pro Arg Asn Glu Thr Arg			
40	5060	5065	5070	
	Val Pro Cys Ser Thr Val Pro Val Thr Thr Glu Val Ser Tyr Ala Gly			
	5075	5080	5085	
45	Cys Thr Lys Thr Val Leu Met Asn His Cys Ser Gly Ser Cys Gly Thr			
	5090	5095	5100	
50	Phe Val Met Tyr Ser Ala Lys Ala Gln Ala Leu Asp His Ser Cys Ser			
	5105	5110	5115	5120
	Cys Cys Lys Glu Glu Lys Thr Ser Gln Arg Glu Val Val Leu Ser Cys			
55	5125	5130	5135	



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Pro Asn Gly Gly Ser Leu Thr His Thr Tyr Thr His Ile Glu Ser Cys  
5 5140 5145 5150  
Gln Cys Gln Asp Thr Val Cys Gly Leu Pro Thr Gly Thr Ser Arg Arg  
5155 5160 5165  
10 Ala Arg Arg Ser Pro Arg His Leu Gly Ser Gly  
5170 5175  
15  
20  
<210> 122  
<211> 1217  
25 <212> PRT  
<213> Homo sapiens  
30  
<400> 122  
Ile Thr Ile Thr Glu Thr Thr Ser His Ser Thr Pro Ser Tyr Thr Thr  
1 5 10 15  
35 Ser Ile Thr Thr Thr Glu Thr Pro Ser His Ser Thr Pro Ser Tyr Thr  
20 25 30  
40 Thr Ser Ile Thr Thr Thr Glu Thr Pro Ser His Ser Thr Pro Ser Phe  
35 40 45  
Thr Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser His Ser Thr Pro Ser  
45 50 55 60  
Phe Thr Ser Ser Ile Arg Thr Thr Glu Thr Thr Ser Tyr Ser Thr Pro  
65 70 75 80  
50 Ser Phe Thr Ser Ser Asn Thr Ile Thr Glu Thr Thr Ser His Ser Thr  
85 90 95  
55 Pro Ser Tyr Ile Thr Ser Ile Thr Thr Thr Glu Thr Pro Ser Ser Ser

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	100	105	110
5	Thr Pro Ser Phe Ser Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser His		
	115	120	125
	Ser Thr Pro Gly Phe Thr Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser		
10	130	135	140
	His Ser Thr Pro Ser Phe Thr Ser Ser Ile Thr Thr Thr Glu Thr Thr		
	145	150	155
15	Ser His Asp Thr Pro Ser Phe Thr Ser Ser Ile Thr Thr Ser Glu Thr		
	165	170	175
20	Pro Ser His Ser Thr Pro Ser Ser Thr Ser Leu Ile Thr Thr Thr Lys		
	180	185	190
	Thr Thr Ser His Ser Thr Pro Ser Phe Thr Ser Ser Ile Thr Thr Thr		
25	195	200	205
	Glu Thr Thr Ser His Ser Ala Arg Ser Phe Thr Ser Ser Ile Thr Thr		
	210	215	220
30	Thr Glu Thr Thr Ser His Asn Thr Arg Ser Phe Thr Ser Ser Ile Thr		
	225	230	235
	Thr Thr Glu Thr Asn Ser His Ser Thr Thr Ser Phe Thr Ser Ser Ile		
35	245	250	255
	Thr Thr Thr Glu Thr Thr Ser His Ser Thr Pro Ser Phe Ser Ser Ser		
40	260	265	270
	Ile Thr Thr Thr Glu Thr Pro Leu His Ser Thr Pro Gly Leu Thr Ser		
	275	280	285
45	Trp Val Thr Thr Thr Lys Thr Thr Ser His Ile Thr Pro Gly Leu Thr		
	290	295	300
	Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser His Ser Thr Pro Gly Phe		
50	305	310	315
	Thr Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser Glu Ser Thr Pro Ser		
55	325	330	335

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Leu Ser Ser Ser Thr Ile Tyr Ser Thr Val Ser Thr Ser Thr Thr Ala  
 5                   340                   345                   350  
 Ile Thr Ser His Phe Thr Thr Ser Glu Thr Ala Val Thr Pro Thr Pro  
                   355                   360                   365  
 10 Val Thr Pro Ser Ser Leu Ser Thr Asp Ile Pro Thr Thr Ser Leu Arg  
           370                   375                   380  
 Thr Leu Thr Pro Ser Ser Val Gly Thr Ser Thr Ser Leu Thr Thr Thr  
 15 385                   390                   395                   400  
 Thr Asp Phe Pro Ser Ile Pro Thr Asp Ile Ser Thr Leu Pro Thr Arg  
                   405                   410                   415  
 20 Thr His Ile Ile Ser Ser Ser Pro Ser Ile Gln Ser Thr Glu Thr Ser  
                   420                   425                   430  
 25 Ser Leu Val Gly Thr Thr Ser Pro Thr Met Ser Thr Val Arg Met Thr  
           435                   440                   445  
 Leu Arg Ile Thr Glu Asn Thr Pro Ile Ser Ser Phe Ser Thr Ser Ile  
 30 450                   455                   460  
 Val Val Ile Pro Glu Thr Pro Thr Gln Thr Pro Pro Val Leu Thr Ser  
 35 465                   470                   475                   480  
 Ala Thr Gly Thr Gln Thr Ser Pro Ala Pro Thr Thr Val Thr Phe Gly  
                   485                   490                   495  
 40 Ser Thr Asp Ser Ser Thr Ser Thr Leu His Thr Leu Thr Pro Ser Thr  
                   500                   505                   510  
 Ala Leu Ser Thr Ile Val Ser Thr Ser Gln Val Pro Ile Pro Ser Thr  
 45 515                   520                   525  
 His Ser Ser Thr Leu Gln Thr Thr Pro Ser Thr Pro Ser Leu Gln Thr  
           530                   535                   540  
 50 Ser Leu Thr Ser Thr Ser Glu Phe Thr Thr Glu Ser Phe Thr Arg Gly  
 545                   550                   555                   560  
 55 Ser Thr Ser Thr Asn Ala Ile Leu Thr Ser Phe Ser Thr Ile Ile Trp

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	565	570	575
5	Ser Ser Thr Pro Thr Ile Ile Met Ser Ser Ser Pro Ser Ser Ala Ser		
	580	585	590
	Ile Thr Pro Val Phe Ser Thr Thr Ile His Ser Val Pro Ser Ser Pro		
10	595	600	605
	Tyr Ile Phe Ser Thr Glu Asn Val Gly Ser Ala Ser Ile Thr Gly Phe		
	610	615	620
15	Pro Ser Leu Ser Ser Ser Ala Thr Thr Ser Thr Ser Ser Thr Ser Ser		
	625	630	635
20	Ser Leu Thr Thr Ala Leu Thr Glu Ile Thr Pro Phe Ser Tyr Ile Ser		
	645	650	655
	Leu Pro Ser Thr Thr Pro Cys Pro Gly Thr Ile Thr Ile Thr Ile Val		
25	660	665	670
	Pro Ala Ser Pro Thr Asp Pro Cys Val Glu Met Asp Pro Ser Thr Glu		
	675	680	685
30	Ala Thr Ser Pro Pro Thr Thr Pro Leu Thr Val Phe Pro Phe Thr Thr		
	690	695	700
	Glu Met Val Thr Cys Pro Thr Ser Ile Ser Ile Gln Thr Thr Leu Thr		
35	705	710	715
	Thr Tyr Met Asp Thr Ser Ser Met Met Pro Glu Ser Glu Ser Ser Ile		
40	725	730	735
	Ser Pro Asn Ala Ser Ser Ser Thr Gly Thr Gly Thr Val Pro Thr Asn		
	740	745	750
45	Thr Val Phe Thr Ser Thr Arg Leu Pro Thr Ser Glu Thr Trp Leu Ser		
	755	760	765
	Asn Ser Ser Val Ile Pro Leu Pro Leu Pro Gly Val Ser Thr Ile Pro		
50	770	775	780
	Leu Thr Met Lys Pro Ser Ser Ser Leu Pro Thr Ile Leu Arg Thr Ser		
55	785	790	795
			800

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	Ser	Lys	Ser	Thr	His	Pro	Ser	Pro	Pro	Thr	Thr	Arg	Thr	Ser	Glu	Thr
5						805				810					815	
	Pro	Val	Ala	Thr	Thr	Gln	Thr	Pro	Thr	Thr	Leu	Thr	Ser	Arg	Arg	Thr
						820				825					830	
10	Thr	Arg	Ile	Thr	Ser	Gln	Met	Thr	Thr	Gln	Ser	Thr	Leu	Thr	Thr	Thr
						835				840					845	
	Ala	Gly	Thr	Cys	Asp	Asn	Gly	Gly	Thr	Trp	Glu	Gln	Gly	Gln	Cys	Ala
15						850				855					860	
	Cys	Leu	Pro	Gly	Phe	Ser	Gly	Asp	Arg	Cys	Gln	Leu	Gln	Thr	Arg	Cys
20						865				870					875	
	Gln	Asn	Gly	Gly	Gln	Trp	Asp	Gly	Leu	Lys	Cys	Gln	Cys	Pro	Ser	Thr
						885				890					895	
25	Phe	Tyr	Gly	Ser	Ser	Cys	Glu	Phe	Ala	Val	Glu	Gln	Val	Asp	Leu	Asp
						900				905					910	
	Val	Val	Glu	Thr	Glu	Val	Gly	Met	Glu	Val	Ser	Val	Asp	Gln	Gln	Phe
30						915				920					925	
	Ser	Pro	Asp	Leu	Asn	Asp	Asn	Thr	Ser	Gln	Ala	Tyr	Arg	Asp	Phe	Asn
35						930				935					940	
	Lys	Thr	Phe	Trp	Asn	Gln	Met	Gln	Lys	Ile	Phe	Ala	Asp	Met	Gln	Gly
						945				950					955	
40	Phe	Thr	Phe	Lys	Gly	Val	Glu	Ile	Leu	Ser	Leu	Arg	Asn	Gly	Ser	Ile
						965				970					975	
	Val	Val	Asp	Tyr	Leu	Val	Leu	Leu	Glu	Met	Pro	Phe	Ser	Pro	Gln	Leu
45						980				985					990	
	Glu	Ser	Glu	Tyr	Glu	Gln	Val	Lys	Thr	Thr	Leu	Lys	Glu	Gly	Leu	Gln
50						995				1000					1005	
	Asn	Ala	Ser	Gln	Asp	Val	Asn	Ser	Cys	Gln	Asp	Ser	Gln	Thr	Leu	Cys
						1010				1015					1020	
55	Phe	Lys	Pro	Asp	Ser	Ile	Lys	Val	Asn	Asn	Asn	Ser	Lys	Thr	Glu	Leu

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1025                      1030                      1035                      1040  
5      Thr Pro Ala Ala Ile Cys Arg Arg Ala Ala Pro Thr Gly Tyr Glu Glu  
                         1045                      1050                      1055  
Phe Tyr Phe Pro Leu Val Glu Ala Thr Arg Leu Arg Cys Val Thr Lys  
10                      1060                      1065                      1070  
Cys Thr Ser Gly Val Asp Asn Ala Ile Asp Cys His Gln Gly Gln Cys  
                         1075                      1080                      1085  
15      Val Leu Glu Thr Ser Gly Pro Thr Cys Arg Cys Tyr Ser Thr Asp Thr  
                         1090                      1095                      1100  
20      His Trp Phe Ser Gly Pro Arg Cys Glu Val Ala Val His Trp Arg Ala  
1105                      1110                      1115                      1120  
Leu Val Gly Gly Leu Thr Ala Gly Ala Ala Leu Leu Val Leu Leu Leu  
25                      1125                      1130                      1135  
Leu Ala Leu Gly Val Arg Ala Val Arg Ser Gly Trp Trp Gly Gly Gln  
                         1140                      1145                      1150  
30      Arg Arg Gly Arg Ser Trp Asp Gln Asp Arg Lys Trp Phe Glu Thr Trp  
                         1155                      1160                      1165  
35      Asp Glu Glu Val Val Gly Thr Phe Ser Asn Trp Gly Phe Glu Asp Asp  
1170                      1175                      1180  
Gly Thr Asp Lys Asp Thr Asn Phe Tyr Val Ala Leu Glu Asn Val Asp  
40      1185                      1190                      1195                      1200  
Thr Thr Met Lys Val His Ile Lys Arg Pro Glu Met Thr Ser Ser Ser  
                         1205                      1210                      1215  
45      Val

<210> 123

55      <211> 1373

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 123

5  
 10 Met Ser Val Gly Arg Arg Lys Leu Ala Leu Leu Trp Ala Leu Ala Leu  
 1 5 10 15  
 15 Ala Leu Ala Cys Thr Arg His Thr Gly His Ala Gln Asp Gly Ser Ser  
 20 25 30  
 25 Glu Ser Ser Tyr Lys His His Pro Ala Leu Ser Pro Ile Ala Arg Gly  
 35 40 45  
 30 Pro Ile Gly Val Pro Leu Arg Gly Ala Thr Val Phe Pro Ser Leu Arg  
 50 55 60  
 35 Thr Ile Pro Val Val Arg Ala Ser Asn Pro Ala His Asn Gly Arg Val  
 65 70 75 80  
 40 Cys Ser Thr Trp Gly Ser Phe His Tyr Lys Thr Phe Asp Gly Asp Val  
 85 90 95  
 45 Phe Arg Phe Pro Gly Leu Cys Asn Tyr Val Phe Ser Glu His Cys Gly  
 100 105 110  
 50 Ala Ala Tyr Glu Asp Phe Asn Ile Pro Ala Thr Pro Gln Pro Gly Val  
 115 120 125  
 55 Ser Gly Pro His Ala Glu Gln Gly Pro His Glu Gly Gly Trp Arg Gly  
 130 135 140  
 60 His Pro Ala Asp Gln Gly Leu Arg Pro Gly Gln Arg Pro Pro Gly Pro  
 145 150 155 160  
 65 Ala Ala Leu Gln Pro Val Trp Gly Pro His Ser Ala Arg Ala Ala Ala  
 165 170 175  
 70 Thr Pro Arg Trp Lys Pro Gly Trp Ala Leu Ser Ser Cys Gly Thr Thr  
 180 185 190  
 75 Met Thr Ala Cys Cys Trp Lys Leu Asp Thr Lys Tyr Ala Asn Lys Asn

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	195	200	205	
5	Leu Trp Ala Leu Trp Gly Leu Gln Arg Asp Ala Arg Gly Gln Arg Ala			
	210	215	220	
	Pro Leu Pro Gln His Gln Ala Asp Thr His Gly Ile Arg Glu Pro Ala			
10	225	230	235	240
	Glu Arg Trp Thr Asn Pro Arg Ser Ser Val Arg Thr Leu Ser Leu Asn			
	245	250	255	
15	Pro Arg Arg Thr Ala Pro Leu Ala Leu Ala Ser Cys Glu Glu Leu Leu			
	260	265	270	
20	His Gly Gln Leu Phe Ser Gly Cys Val Ala Leu Val Asp Val Gly Ser			
	275	280	285	
	Tyr Leu Glu Ala Cys Arg Gln Asp Leu Cys Phe Cys Glu Asp Thr Asp			
25	290	295	300	
	Leu Leu Ser Cys Val Cys His Thr Leu Ala Glu Tyr Ser Arg Gln Cys			
	305	310	315	320
30	Thr His Ala Gly Gly Leu Pro Gln Asp Trp Arg Gly Pro Asp Phe Cys			
	325	330	335	
35	Pro Gln Lys Cys Pro Asn Asn Met Gln Tyr His Glu Cys Arg Ser Pro			
	340	345	350	
	Cys Ala Asp Thr Cys Ser Asn Gln Glu His Ser Arg Ala Cys Glu Asp			
40	355	360	365	
	His Cys Val Ala Gly Cys Phe Cys Pro Glu Gly Thr Val Leu Asp Asp			
	370	375	380	
45	Ile Gly Gln Thr Gly Cys Val Pro Val Ser Lys Cys Ala Cys Val Tyr			
	385	390	395	400
	Asn Gly Ala Ala Tyr Ala Pro Gly Ala Thr Tyr Ser Thr Asp Cys Thr			
50	405	410	415	
	Asn Cys Thr Cys Ser Gly Gly Arg Trp Ser Cys Gln Glu Val Pro Cys			
55	420	425	430	



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Pro Gly Thr Cys Ser Val Leu Gly Gly Ala His Phe Ser Thr Phe Asp  
5 435 440 445  
Gly Lys Gln Tyr Thr Val His Gly Asp Cys Ser Tyr Val Leu Thr Lys  
450 455 460  
10 Pro Cys Asp Ser Ser Ala Phe Thr Val Leu Ala Glu Leu Arg Arg Cys  
465 470 475 480  
Gly Leu Thr Asp Ser Glu Thr Cys Leu Lys Ser Val Thr Leu Ser Leu  
15 485 490 495  
Asp Gly Ala Gln Thr Val Val Val Ile Lys Ala Ser Gly Glu Val Phe  
20 500 505 510  
Leu Asn Gln Ile Tyr Thr Gln Leu Pro Ile Ser Ala Ala Asn Val Thr  
515 520 525  
25 Ile Phe Arg Pro Ser Thr Phe Phe Ile Ile Ala Gln Thr Ser Leu Gly  
530 535 540  
Leu Gln Leu Asn Leu Gln Leu Val Pro Thr Met Gln Leu Phe Met Gln  
30 545 550 555 560  
Leu Ala Pro Lys Leu Arg Gly Gln Thr Cys Gly Leu Cys Gly Asn Phe  
35 565 570 575  
Asn Ser Ile Gln Ala Asp Asp Phe Arg Thr Leu Ser Gly Val Val Glu  
580 585 590  
40 Ala Thr Ala Ala Ala Phe Phe Asn Thr Phe Lys Thr Gln Ala Ala Cys  
595 600 605  
Pro Asn Ile Arg Asn Ser Phe Glu Asp Pro Cys Ser Leu Ser Val Glu  
45 610 615 620  
Asn Glu Lys Tyr Ala Gln His Trp Cys Ser Gln Leu Thr Asp Ala Asp  
50 625 630 635 640  
Gly Pro Phe Gly Arg Cys His Ala Ala Val Lys Pro Gly Thr Tyr Tyr  
645 650 655  
55 Ser Asn Cys Met Phe Asp Thr Cys Asn Cys Glu Arg Ser Glu Asp Cys

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	660	665	670
5	Leu Cys Ala Ala Leu Ser Ser Tyr Val His Ala Cys Ala Ala Lys Gly		
	675	680	685
	Val Gln Leu Gly Gly Trp Arg Asp Gly Val Cys Thr Lys Pro Met Thr		
10	690	695	700
	Thr Cys Pro Lys Ser Met Thr Tyr His Tyr His Val Ser Thr Cys Gln		
	705	710	715
15	Pro Thr Cys Arg Ser Leu Ser Glu Gly Asp Ile Thr Cys Ser Val Gly		
	725	730	735
20	Phe Ile Pro Val Asp Gly Cys Ile Cys Pro Lys Gly Thr Phe Leu Asp		
	740	745	750
	Asp Thr Gly Lys Cys Val Gln Ala Ser Asn Cys Pro Cys Tyr His Arg		
25	755	760	765
	Gly Ser Met Ile Pro Asn Gly Glu Ser Val His Asp Ser Gly Ala Ile		
	770	775	780
30	Cys Thr Cys Thr His Gly Lys Leu Ser Cys Ile Gly Gly Gln Ala Pro		
	785	790	795
	Ala Pro Val Cys Ala Ala Pro Met Val Phe Phe Asp Cys Arg Asn Ala		
35	805	810	815
	Thr Pro Gly Asp Thr Gly Ala Gly Cys Gln Lys Ser Cys His Thr Leu		
40	820	825	830
	Asp Met Thr Cys Tyr Ser Pro Gln Cys Val Pro Gly Cys Val Cys Pro		
	835	840	845
45	Asp Gly Leu Val Ala Asp Gly Glu Gly Gly Cys Ile Thr Ala Glu Asp		
	850	855	860
	Cys Pro Cys Val His Asn Glu Ala Ser Tyr Arg Ala Gly Gln Thr Ile		
50	865	870	875
	Arg Val Gly Cys Asn Thr Cys Thr Cys Asp Ser Arg Met Trp Arg Cys		
55	885	890	895

Thr Asp Asp Pro Cys Leu Ala Thr Cys Ala Val Tyr Gly Asp Gly His  
 5                   900                   905                   910  
 Tyr Leu Thr Phe Asp Gly Gln Ser Tyr Ser Phe Asn Glu Glu Thr Ala  
                   915                   920                   925  
 10 Ser Thr Arg Trp Cys Arg Thr Ala Val Ala Gly Lys Thr Ala Pro Arg  
                   930                   935                   940  
 Thr Pro Phe Val Leu Ser Pro Arg Thr Ser Pro Ala Ala Pro Gln Gly  
 15 945                   950                   955                   960  
 Pro Pro Ala Pro Arg Pro Ser Arg Phe Ser Trp Gly Asn Phe Glu Leu  
 20                   965                   970                   975  
 Lys Leu Ser His Gly Lys Val Glu Val Ile Gly Thr Asp Glu Ser Gln  
                   980                   985                   990  
 25 Glu Val Pro Tyr Thr Ile Arg Gln Met Gly Ile Tyr Leu Val Val Asp  
                   995                   1000                   1005  
 Thr Asp Ile Gly Leu Val Leu Leu Trp Asp Lys Lys Thr Ser Ile Phe  
 30                   1010                   1015                   1020  
 Ile Asn Leu Ser Pro Glu Phe Lys Gly Arg Val Cys Gly Leu Cys Gly  
 35 1025                   1030                   1035                   1040  
 Asn Phe Asp Asp Ile Ala Val Asn Asp Phe Ala Thr Arg Ser Arg Ser  
                   1045                   1050                   1055  
 40 Val Val Gly Asp Val Leu Glu Phe Gly Asn Ser Trp Lys Leu Ser Pro  
                   1060                   1065                   1070  
 Ser Cys Pro Asp Ala Leu Ala Pro Lys Asp Pro Cys Thr Ala Asn Pro  
 45                   1075                   1080                   1085  
 Phe Arg Lys Ser Trp Ala Gln Lys Gln Cys Ser Ile Leu His Gly Pro  
 50                   1090                   1095                   1100  
 Thr Phe Ala Ala Cys His Ala His Val Glu Pro Ala Arg Tyr Tyr Glu  
                   1105                   1110                   1115                   1120  
 55 Ala Cys Val Asn Asp Ala Cys Ala Cys Asp Ser Gly Gly Asp Cys Glu

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	1125	1130	1135
5	Cys Phe Cys Thr Ala Val Ala Arg Tyr Ala Gln Ala Cys His Glu Val		
	1140	1145	1150
	Gly Thr Cys Val Cys Leu Arg Thr Pro Ser Ile Cys Pro Leu Phe Cys		
10	1155	1160	1165
	Asp Tyr Tyr Asn Pro Glu Gly Gln Cys Glu Trp His Tyr Gln Pro Cys		
	1170	1175	1180
15	Gly Val Pro Cys Leu Arg Thr Cys Arg Asn Pro Arg Gly Asp Cys Leu		
	1185	1190	1195
	Arg Asp Val Arg Gly Leu Glu Gly Cys Tyr Pro Lys Cys Pro Pro Glu		
20	1205	1210	1215
	Ala Pro Ile Phe Asp Glu Asp Lys Met Gln Cys Val Ala Thr Cys Pro		
25	1220	1225	1230
	Thr Pro Pro Leu Pro Pro Arg Cys His Val His Gly Lys Ser Tyr Arg		
	1235	1240	1245
30	Pro Gly Ala Val Val Pro Ser Asp Lys Asn Cys Gln Ser Cys Leu Cys		
	1250	1255	1260
	Thr Glu Arg Gly Val Glu Cys Thr Tyr Lys Ala Glu Ala Cys Val Cys		
35	1265	1270	1275
	Thr Tyr Asn Gly Gln Arg Phe His Pro Gly Asp Val Ile Tyr His Thr		
40	1285	1290	1295
	Thr Asp Gly Thr Gly Gly Cys Ile Ser Ala Arg Cys Gly Ala Asn Gly		
	1300	1305	1310
45	Thr Ile Glu Arg Arg Val Tyr Pro Cys Ser Pro Thr Thr Pro Val Pro		
	1315	1320	1325
	Pro Thr Thr Phe Ser Phe Ser Thr Pro Pro Leu Val Val Ser Ser Thr		
50	1330	1335	1340
	His Thr Pro Ser Asn Gly Pro Ser Ser Ala His Thr Gly Pro Pro Ser		
55	1345	1350	1355
	1360		

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Ser Ala Trp Pro Thr Thr Ala Gly Thr Ser Pro Arg Thr  
5 1365 1370

10 <210> 124  
<211> 165  
<212> PRT  
15 <213> Homo sapiens

20 <400> 124  
Met Glu Met Phe Gln Gly Leu Leu Leu Leu Leu Leu Ser Met Gly  
1 5 10 15  
25 Gly Thr Trp Ala Ser Lys Glu Pro Leu Arg Pro Arg Cys Arg Pro Ile  
20 25 30  
Asn Ala Thr Leu Ala Val Glu Lys Glu Gly Cys Pro Val Cys Ile Thr  
30 35 40 45  
Val Asn Thr Thr Ile Cys Ala Gly Tyr Cys Pro Thr Met Thr Arg Val  
50 55 60  
35 Leu Gln Gly Val Leu Pro Ala Leu Pro Gln Val Val Cys Asn Tyr Arg  
65 70 75 80  
40 Asp Val Arg Phe Glu Ser Ile Arg Leu Pro Gly Cys Pro Arg Gly Val  
85 90 95  
Asn Pro Val Val Ser Tyr Ala Val Ala Leu Ser Cys Gln Cys Ala Leu  
45 100 105 110  
Cys Arg Arg Ser Thr Thr Asp Cys Gly Gly Pro Lys Asp His Pro Leu  
115 120 125  
50 Thr Cys Asp Asp Pro Arg Phe Gln Asp Ser Ser Ser Ser Lys Ala Pro  
130 135 140  
55 Pro Pro Ser Leu Pro Ser Pro Ser Arg Leu Pro Gly Pro Ser Asp Thr

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145 150 155 160

5 Pro Ile Leu Pro Gln

165

10

<210> 125

<211> 1210

15 <212> PRT

<213> Homo sapiens

20

<400> 125

Met Arg Pro Ser Gly Thr Ala Gly Ala Ala Leu Leu Ala Leu Leu Ala

25 1 5 10 15

Ala Leu Cys Pro Ala Ser Arg Ala Leu Glu Glu Lys Lys Val Cys Gln

20 25 30

30 Gly Thr Ser Asn Lys Leu Thr Gln Leu Gly Thr Phe Glu Asp His Phe

35 40 45

Leu Ser Leu Gln Arg Met Phe Asn Asn Cys Glu Val Val Leu Gly Asn

50 55 60

Leu Glu Ile Thr Tyr Val Gln Arg Asn Tyr Asp Leu Ser Phe Leu Lys

40 65 70 75 80

Thr Ile Gln Glu Val Ala Gly Tyr Val Leu Ile Ala Leu Asn Thr Val

85 90 95

45 Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg Gly Asn Met Tyr

100 105 110

Tyr Glu Asn Ser Tyr Ala Leu Ala Val Leu Ser Asn Tyr Asp Ala Asn

50 115 120 125

Lys Thr Gly Leu Lys Glu Leu Pro Met Arg Asn Leu Gln Glu Ile Leu

55 130 135 140

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His Gly Ala Val Arg Phe Ser Asn Asn Pro Ala Leu Cys Asn Val Glu  
 5 145 150 155 160  
 Ser Ile Gln Trp Arg Asp Ile Val Ser Ser Asp Phe Leu Ser Asn Met  
 165 170 175  
 10 Ser Met Asp Phe Gln Asn His Leu Gly Ser Cys Gln Lys Cys Asp Pro  
 180 185 190  
 Ser Cys Pro Asn Gly Ser Cys Trp Gly Ala Gly Glu Glu Asn Cys Gln  
 15 195 200 205  
 Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser Gly Arg Cys Arg  
 20 210 215 220  
 Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys Ala Ala Gly Cys  
 225 230 235 240  
 25 Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg Lys Phe Arg Asp  
 245 250 255  
 Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met Leu Tyr Asn Pro  
 30 260 265 270  
 Thr Thr Tyr Gln Met Asp Val Asn Pro Glu Gly Lys Tyr Ser Phe Gly  
 275 280 285  
 35 Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr Val Val Thr Asp His  
 290 295 300  
 40 Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser Tyr Glu Met Glu Glu  
 305 310 315 320  
 Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly Pro Cys Arg Lys Val  
 45 325 330 335  
 Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser Ile Asn  
 340 345 350  
 50 Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser Gly Asp  
 355 360 365  
 55 Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe Thr His Thr

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	370	375	380	
5	Pro Pro Leu Asp	Pro Gln Glu Leu Asp	Ile Leu Lys Thr Val Lys Glu	
	385	390	395	400
	Ile Thr Gly Phe	Leu Leu Ile Gln Ala Trp	Pro Glu Asn Arg Thr Asp	
10		405	410	415
	Leu His Ala Phe	Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr Lys Gln		
		420	425	430
15	His Gly Gln Phe	Ser Leu Ala Val Val Ser Leu Asn Ile Thr Ser Leu		
		435	440	445
20	Gly Leu Arg Ser	Leu Lys Glu Ile Ser Asp Gly Asp Val Ile Ile Ser		
		450	455	460
	Gly Asn Lys Asn	Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys Lys Leu		
25		465	470	475
	Phe Gly Thr Ser	Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg Gly Glu		
		485	490	495
30	Asn Ser Cys Lys	Ala Thr Gly Gln Val Cys His Ala Leu Cys Ser Pro		
		500	505	510
35	Glu Gly Cys Trp	Gly Pro Glu Pro Arg Asp Cys Val Ser Cys Arg Asn		
		515	520	525
	Val Ser Arg Gly	Arg Glu Cys Val Asp Lys Cys Lys Leu Leu Glu Gly		
40		530	535	540
	Glu Pro Arg Glu	Phe Val Glu Asn Ser Glu Cys Ile Gln Cys His Pro		
		545	550	555
45	Glu Cys Leu Pro	Gln Ala Met Asn Ile Thr Cys Thr Gly Arg Gly Pro		
		565	570	575
	Asp Asn Cys Ile	Gln Cys Ala His Tyr Ile Asp Gly Pro His Cys Val		
50		580	585	590
	Lys Thr Cys Pro	Ala Gly Val Met Gly Glu Asn Asn Thr Leu Val Trp		
55		595	600	605



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Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro Asn Cys  
 5           610                   615                   620  
 Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr Asn Gly  
 625                   630                   635                   640  
 10   Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu Leu  
           645                   650                   655  
 Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg Arg His  
 15                   660                   665                   670  
 Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu Gln Glu Arg Glu Leu  
 20           675                   680                   685  
 Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro Asn Gln Ala Leu Leu  
           690                   695                   700  
 25   Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile Lys Val Leu Gly Ser  
 705                   710                   715                   720  
 Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp Ile Pro Glu Gly Glu  
 30                   725                   730                   735  
 Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu Arg Glu Ala Thr Ser  
           740                   745                   750  
 35   Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Ser  
           755                   760                   765  
 40   Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu Thr Ser  
           770                   775                   780  
 Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe Gly Cys Leu Leu Asp  
 45   785                   790                   795                   800  
 Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser Gln Tyr Leu Leu Asn  
           805                   810                   815  
 50   Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr Leu Glu Asp Arg Arg  
           820                   825                   830  
 55   Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Thr Pro

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	835	840	845	
5	Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala Lys Leu Leu Gly Ala			
	850	855	860	
	Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys Val Pro Ile Lys Trp			
10	865	870	875	880
	Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln Ser Asp			
	885	890	895	
15	Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ser			
	900	905	910	
20	Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile Ser Ser Ile Leu Glu			
	915	920	925	
	Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr			
25	930	935	940	
	Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg Pro Lys			
	945	950	955	960
30	Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp Pro Gln			
	965	970	975	
	Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro Ser Pro			
35	980	985	990	
	Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp Met Asp			
40	995	1000	1005	
	Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln Gly Phe Phe			
	1010	1015	1020	
45	Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu Ser Ser Leu Ser Ala			
	1025	1030	1035	1040
	Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp Arg Asn Gly Leu Gln			
50	1045	1050	1055	
	Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln Arg Tyr Ser Ser Asp			
55	1060	1065	1070	

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Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp Asp Thr Phe Leu Pro  
5                   1075                   1080                   1085  
Val Pro Glu Tyr Ile Asn Gln Ser Val Pro Lys Arg Pro Ala Gly Ser  
                  1090                   1095                   1100  
10 Val Gln Asn Pro Val Tyr His Asn Gln Pro Leu Asn Pro Ala Pro Ser  
1105                   1110                   1115                   1120  
Arg Asp Pro His Tyr Gln Asp Pro His Ser Thr Ala Val Gly Asn Pro  
15                   1125                   1130                   1135  
Glu Tyr Leu Asn Thr Val Gln Pro Thr Cys Val Asn Ser Thr Phe Asp  
                  1140                   1145                   1150  
20 Ser Pro Ala His Trp Ala Gln Lys Gly Ser His Gln Ile Ser Leu Asp  
                  1155                   1160                   1165  
25 Asn Pro Asp Tyr Gln Gln Asp Phe Phe Pro Lys Glu Ala Lys Pro Asn  
1170                   1175                   1180  
Gly Ile Phe Lys Gly Ser Thr Ala Glu Asn Ala Glu Tyr Leu Arg Val  
30 1185                   1190                   1195                   1200  
Ala Pro Gln Ser Ser Glu Phe Ile Gly Ala  
                  1205                   1210  
35  
40 <210> 126  
<211> 1255  
<212> PRT  
45 <213> Homo sapiens  
  
50 <400> 126  
Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu  
1                   5                   10                   15  
55 Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys

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	20	25	30
5	Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His		
	35	40	45
	Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr		
10	50	55	60
	Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val		
	65	70	75
15	Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu		
	85	90	95
	Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr		
20	100	105	110
	Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro		
25	115	120	125
	Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser		
	130	135	140
30	Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln		
	145	150	155
	Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn		
35	165	170	175
	Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys		
40	180	185	190
	His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser		
	195	200	205
45	Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys		
	210	215	220
	Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys		
50	225	230	235
	Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu		
55	245	250	255

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His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val  
260 265 270  
5 Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg  
275 280 285  
10 Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu  
290 295 300  
Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln  
15 305 310 315 320  
Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys  
325 330 335  
20 Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu  
340 345 350  
25 Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys  
355 360 365  
Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp  
30 370 375 380  
Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe  
385 390 395 400  
35 Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro  
405 410 415  
40 Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg  
420 425 430  
Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu  
45 435 440 445  
Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly  
450 455 460  
50 Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val  
465 470 475 480  
55 Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr

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	485	490	495
5	Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His		
	500	505	510
	Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys		
10	515	520	525
	Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys		
	530	535	540
15	Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys		
	545	550	555
	Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys		
20	565	570	575
	Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp		
25	580	585	590
	Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu		
	595	600	605
30	Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln		
	610	615	620
	Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys		
35	625	630	635
	Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile Val Ser		
40	645	650	655
	Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val Phe Gly		
	660	665	670
45	Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg		
	675	680	685
	Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly		
50	690	695	700
	Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu Leu		
55	705	710	715
			720

Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys  
 5                               725                               730                               735  
 Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala Ile  
                               740                               745                               750  
 10 Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu  
                               755                               760                               765  
 Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser Arg  
 15                               770                               775                               780  
 Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln Leu  
 20 785                               790                               795                               800  
 Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn Arg Gly Arg  
                               805                               810                               815  
 25 Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala Lys Gly  
                               820                               825                               830  
 Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu Ala Ala  
 30                               835                               840                               845  
 Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe  
                               850                               855                               860  
 35 Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp  
 865                               870                               875                               880  
 40 Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg  
                               885                               890                               895  
 Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val  
 45                               900                               905                               910  
 Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala  
                               915                               920                               925  
 50 Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro  
                               930                               935                               940  
 55 Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met

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	945	950	955	960
5	Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe			
		965	970	975
	Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu			
10		980	985	990
	Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu			
		995	1000	1005
15	Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr Leu			
		1010	1015	1020
20	Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro Ala Pro Gly Ala Gly			
		1025	1030	1035
	Gly Met Val His His Arg His Arg Ser Ser Ser Thr Arg Ser Gly Gly			
25		1045	1050	1055
	Gly Asp Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu Glu Ala Pro Arg			
		1060	1065	1070
30	Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser Asp Val Phe Asp Gly			
		1075	1080	1085
35	Asp Leu Gly Met Gly Ala Ala Lys Gly Leu Gln Ser Leu Pro Thr His			
		1090	1095	1100
	Asp Pro Ser Pro Leu Gln Arg Tyr Ser Glu Asp Pro Thr Val Pro Leu			
40		1105	1110	1115
	Pro Ser Glu Thr Asp Gly Tyr Val Ala Pro Leu Thr Cys Ser Pro Gln			
		1125	1130	1135
45	Pro Glu Tyr Val Asn Gln Pro Asp Val Arg Pro Gln Pro Pro Ser Pro			
		1140	1145	1150
	Arg Glu Gly Pro Leu Pro Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu			
50		1155	1160	1165
	Arg Ala Lys Thr Leu Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val			
55		1170	1175	1180



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Phe Ala Phe Gly Gly Ala Val Glu Asn Pro Glu Tyr Leu Thr Pro Gln  
 1185 1190 1195 1200  
 Gly Gly Ala Ala Pro Gln Pro His Pro Pro Pro Ala Phe Ser Pro Ala  
 1205 1210 1215  
 Phe Asp Asn Leu Tyr Tyr Trp Asp Gln Asp Pro Pro Glu Arg Gly Ala  
 1220 1225 1230  
 Pro Pro Ser Thr Phe Lys Gly Thr Pro Thr Ala Glu Asn Pro Glu Tyr  
 1235 1240 1245  
 Leu Gly Leu Asp Val Pro Val  
 1250 1255  
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 Met Thr Thr Ala Ser Thr Ser Gln Val Arg Gln Asn Tyr His Gln Asp  
 1 5 10 15  
 Ser Glu Ala Ala Ile Asn Arg Gln Ile Asn Leu Glu Leu Tyr Ala Ser  
 20 25 30  
 Tyr Val Tyr Leu Ser Met Ser Tyr Tyr Phe Asp Arg Asp Asp Val Ala  
 35 40 45  
 Leu Lys Asn Phe Ala Lys Tyr Phe Leu His Gln Ser His Glu Glu Arg  
 50 55 60  
 Glu His Ala Glu Lys Leu Met Lys Leu Gln Asn Gln Arg Gly Gly Arg  
 65 70 75 80  
 Ile Phe Leu Gln Asp Ile Lys Lys Pro Asp Cys Asp Asp Trp Glu Ser

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85 90 95  
 5 Gly Leu Asn Ala Met Glu Cys Ala Leu His Leu Glu Lys Asn Val Asn  
 100 105 110  
 Gln Ser Leu Leu Glu Leu His Lys Leu Ala Thr Asp Lys Asn Asp Pro  
 10 115 120 125  
 His Leu Cys Asp Phe Ile Glu Thr His Tyr Leu Asn Glu Gln Val Lys  
 130 135 140  
 15 Ala Ile Lys Glu Leu Gly Asp His Val Thr Asn Leu Arg Lys Met Gly  
 145 150 155 160  
 Ala Pro Glu Ser Gly Leu Ala Glu Tyr Leu Phe Asp Lys His Thr Trp  
 20 165 170 175  
 Glu Thr Val Ile Met Lys Ala Lys Pro Arg Ala Asn Phe Pro  
 25 180 185 190  
 30 <210> 128  
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 35 <213> Homo sapiens  
 40 <400> 128  
 Met Ser Ser Gln Ile Arg Gln Asn Tyr Ser Thr Asp Val Glu Ala Ala  
 1 5 10 15  
 45 Val Asn Ser Leu Val Asn Leu Tyr Leu Gln Ala Ser Tyr Thr Tyr Leu  
 20 25 30  
 Ser Leu Gly Phe Tyr Phe Asp Arg Asp Asp Val Ala Leu Glu Gly Val  
 50 35 40 45  
 Ser His Phe Phe Arg Glu Leu Ala Glu Glu Lys Arg Glu Gly Tyr Glu  
 55 50 55 60

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Arg Leu Leu Lys Met Gln Asn Gln Arg Gly Gly Arg Ala Leu Phe Gln
5 65 70 75 80
Asp Ile Lys Lys Pro Ala Glu Asp Glu Trp Gly Lys Thr Pro Asp Ala
85 90 95
10 Met Lys Ala Ala Met Ala Leu Glu Lys Lys Leu Asn Gln Ala Leu Leu
100 105 110
Asp Leu His Ala Leu Gly Ser Ala Arg Thr Asp Pro His Leu Cys Asp
15 115 120 125
Phe Leu Glu Thr His Phe Leu Asp Glu Glu Val Lys Leu Ile Lys Lys
130 135 140
20 Met Gly Asp His Leu Thr Asn Leu His Arg Leu Gly Gly Pro Glu Ala
145 150 155 160
25 Gly Leu Gly Glu Tyr Leu Phe Glu Arg Leu Thr Leu Lys His Asp
165 170 175
30
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35 <212> PRT
<213> Homo sapiens
40
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Met Leu Gly Pro Cys Met Leu Leu Leu Leu Leu Leu Gly Leu Arg
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Leu Gln Leu Ser Leu Gly Ile Ile Leu Val Glu Glu Glu Asn Pro Asp
20 25 30
50 Phe Trp Asn Arg Glu Ala Ala Glu Ala Leu Gly Ala Ala Lys Lys Leu
35 40 45
55 Gln Pro Ala Gln Thr Ala Ala Lys Asn Leu Ile Ile Phe Leu Gly Asp

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	50	55	60	
5	Gly Met Gly Val Ser Thr Val Thr Ala Ala Arg Ile Leu Lys Gly Gln			
	65	70	75	80
	Lys Lys Asp Lys Leu Gly Pro Glu Ile Pro Leu Ala Met Asp Arg Phe			
10		85	90	95
	Pro Tyr Val Ala Leu Ser Lys Thr Tyr Asn Val Asp Lys His Val Pro			
	100	105	110	
15	Asp Ser Gly Ala Thr Ala Thr Ala Tyr Leu Cys Gly Val Lys Gly Asn			
	115	120	125	
20	Phe Gln Thr Ile Gly Leu Ser Ala Ala Ala Arg Phe Asn Gln Cys Asn			
	130	135	140	
	Thr Thr Arg Gly Asn Glu Val Ile Ser Val Met Asn Arg Ala Lys Lys			
25	145	150	155	160
	Ala Gly Lys Ser Val Gly Val Val Thr Thr Thr Arg Val Gln His Ala			
	165	170	175	
30	Ser Pro Ala Gly Thr Tyr Ala His Thr Val Asn Arg Asn Trp Tyr Ser			
	180	185	190	
35	Asp Ala Asp Val Pro Ala Ser Ala Arg Gln Glu Gly Cys Gln Asp Ile			
	195	200	205	
	Ala Thr Gln Leu Ile Ser Asn Met Asp Ile Asp Val Ile Leu Gly Gly			
40	210	215	220	
	Gly Arg Lys Tyr Met Phe Arg Met Gly Thr Pro Asp Pro Glu Tyr Pro			
	225	230	235	240
45	Asp Asp Tyr Ser Gln Gly Gly Thr Arg Leu Asp Gly Lys Asn Leu Val			
	245	250	255	
50	Gln Glu Trp Leu Ala Lys Arg Gln Gly Ala Arg Tyr Val Trp Asn Arg			
	260	265	270	
	Thr Glu Leu Met Gln Ala Ser Leu Asp Pro Ser Val Ala His Leu Met			
55	275	280	285	

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Gly Leu Phe Glu Pro Gly Asp Met Lys Tyr Glu Ile His Arg Asp Ser  
 5           290                           295                           300  
 Thr Leu Asp Pro Ser Leu Met Glu Met Thr Glu Ala Ala Leu Arg Leu  
 305                           310                           315                           320  
 10 Leu Ser Arg Asn Pro Arg Gly Phe Phe Leu Phe Val Glu Gly Gly Arg  
                          325                           330                           335  
 Ile Asp His Gly His His Glu Ser Arg Ala Tyr Arg Ala Leu Thr Glu  
 15                           340                           345                           350  
 Thr Ile Met Phe Asp Asp Ala Ile Glu Arg Ala Gly Gln Leu Thr Ser  
 20                           355                           360                           365  
 Glu Glu Asp Thr Leu Ser Leu Val Thr Ala Asp His Ser His Val Phe  
                          370                           375                           380  
 25 Ser Phe Gly Gly Tyr Pro Leu Arg Gly Ser Ser Ile Phe Gly Leu Ala  
 385                           390                           395                           400  
 Pro Gly Lys Ala Arg Asp Arg Lys Ala Tyr Thr Val Leu Leu Tyr Gly  
 30                           405                           410                           415  
 Asn Gly Pro Gly Tyr Val Leu Lys Asp Gly Ala Arg Pro Asp Val Thr  
                          420                           425                           430  
 35 Glu Ser Glu Ser Gly Ser Pro Glu Tyr Arg Gln Gln Ser Ala Val Pro  
                          435                           440                           445  
 40 Leu Asp Glu Glu Thr His Ala Gly Glu Asp Val Ala Val Phe Ala Arg  
                          450                           455                           460  
 Gly Pro Gln Ala His Leu Val His Gly Val Gln Glu Gln Thr Phe Ile  
 45                           465                           470                           475                           480  
 Ala His Val Met Ala Phe Ala Ala Cys Leu Glu Pro Tyr Thr Ala Cys  
                          485                           490                           495  
 50 Asp Leu Ala Pro Pro Ala Gly Thr Thr Asp Ala Ala His Pro Gly Arg  
                          500                           505                           510  
 55 Ser Val Val Pro Ala Leu Leu Pro Leu Leu Ala Gly Thr Leu Leu Leu

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	515	520	525
5	Leu Glu Thr Ala Thr Ala Pro		
	530	535	
10			
	<210> 130		
	<211> 461		
15	<212> PRT		
	<213> Homo sapiens		
20			
	<400> 130		
	Met Asn Asn Phe Gly Asn Glu Glu Phe Asp Cys His Phe Leu Asp Glu		
25	1	5	10 15
	Gly Phe Thr Ala Lys Asp Ile Leu Asp Gln Lys Ile Asn Glu Val Ser		
	20	25	30
30	Ser Ser Asp Asp Lys Asp Ala Phe Tyr Val Ala Asp Leu Gly Asp Ile		
	35	40	45
35	Leu Lys Lys His Leu Arg Trp Leu Lys Ala Leu Pro Arg Val Thr Pro		
	50	55	60
	Phe Tyr Ala Val Lys Cys Asn Asp Ser Lys Ala Ile Val Lys Thr Leu		
40	65	70	75 80
	Ala Ala Thr Gly Thr Gly Phe Asp Cys Ala Ser Lys Thr Glu Ile Gln		
	85	90	95
45	Leu Val Gln Ser Leu Gly Val Pro Pro Glu Arg Ile Ile Tyr Ala Asn		
	100	105	110
50	Pro Cys Lys Gln Val Ser Gln Ile Lys Tyr Ala Ala Asn Asn Gly Val		
	115	120	125
	Gln Met Met Thr Phe Asp Ser Glu Val Glu Leu Met Lys Val Ala Arg		
55	130	135	140

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Ala His Pro Lys Ala Lys Leu Val Leu Arg Ile Ala Thr Asp Asp Ser  
5 145 150 155 160  
Lys Ala Val Cys Arg Leu Ser Val Lys Phe Gly Ala Thr Leu Arg Thr  
165 170 175  
10 Ser Arg Leu Leu Leu Glu Arg Ala Lys Glu Leu Asn Ile Asp Val Val  
180 185 190  
Gly Val Ser Phe His Val Gly Ser Gly Cys Thr Asp Pro Glu Thr Phe  
15 195 200 205  
Val Gln Ala Ile Ser Asp Ala Arg Cys Val Phe Asp Met Gly Ala Glu  
20 210 215 220  
Val Gly Phe Ser Met Tyr Leu Leu Asp Ile Gly Gly Gly Phe Pro Gly  
225 230 235 240  
25 Ser Glu Asp Val Lys Leu Lys Phe Glu Glu Ile Thr Gly Val Ile Asn  
245 250 255  
Pro Ala Leu Asp Lys Tyr Phe Pro Ser Asp Ser Gly Val Arg Ile Ile  
30 260 265 270  
Ala Glu Pro Gly Arg Tyr Tyr Val Ala Ser Ala Phe Thr Leu Ala Val  
35 275 280 285  
Asn Ile Ile Ala Lys Lys Ile Val Leu Lys Glu Gln Thr Gly Ser Asp  
290 295 300  
40 Asp Glu Asp Glu Ser Ser Glu Gln Thr Phe Met Tyr Tyr Val Asn Asp  
305 310 315 320  
Gly Val Tyr Gly Ser Phe Asn Cys Ile Leu Tyr Asp His Ala His Val  
45 325 330 335  
Lys Pro Leu Leu Gln Lys Arg Pro Lys Pro Asp Glu Lys Tyr Tyr Ser  
340 345 350  
50 Ser Ser Ile Trp Gly Pro Thr Cys Asp Gly Leu Asp Arg Ile Val Glu  
355 360 365  
55 Arg Cys Asp Leu Pro Glu Met His Val Gly Asp Trp Met Leu Phe Glu

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	370	375	380	
5	Asn Met Gly Ala Tyr Thr Val Ala Ala Ala Ser Thr Phe Asn Gly Phe			
	385	390	395	400
	Gln Arg Pro Thr Ile Tyr Tyr Val Met Ser Gly Pro Ala Trp Gln Leu			
10		405	410	415
	Met Gln Gln Phe Gln Asn Pro Asp Phe Pro Pro Glu Val Glu Glu Gln			
	420	425	430	
15	Asp Ala Ser Thr Leu Pro Val Ser Cys Ala Trp Glu Ser Gly Met Lys			
	435	440	445	
20	Arg His Arg Ala Ala Cys Ala Ser Ala Ser Ile Asn Val			
	450	455	460	
25				
	<210> 131			
	<211> 1148			
30	<212> PRT			
	<213> Homo sapiens			
35				
	<400> 131			
	Met Pro Leu Phe Lys Asn Thr Ser Val Ser Ser Leu Tyr Ser Gly Cys			
40	1	5	10	15
	Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Arg Val			
	20	25	30	
45	Asp Ala Val Cys Thr His Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp			
	35	40	45	
	Arg Glu Arg Leu Tyr Trp Lys Leu Ser Gln Leu Thr His Gly Ile Thr			
50	50	55	60	
	Glu Leu Gly Pro Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn Gly			
55	65	70	75	80



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Phe Thr His Gln Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr Ser  
 5                                      85                                      90                                      95  
 Thr Met His Leu Ala Thr Ser Arg Thr Pro Ala Ser Leu Ser Gly Pro  
                                     100                                      105                                      110  
 10 Thr Thr Ala Ser Pro Leu Leu Val Leu Phe Thr Ile Asn Phe Thr Ile  
                                     115                                      120                                      125  
 Thr Asn Leu Arg Tyr Glu Glu Asn Met His His Pro Gly Ser Arg Lys  
 15                                      130                                      135                                      140  
 Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Val Phe  
 20 145                                      150                                      155                                      160  
 Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu  
                                     165                                      170                                      175  
 25 Leu Arg Pro Lys Lys Asp Gly Ala Ala Thr Lys Val Asp Ala Ile Cys  
                                     180                                      185                                      190  
 Thr Tyr Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln Leu  
 30                                      195                                      200                                      205  
 Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro  
 35                                      210                                      215                                      220  
 Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr Gln Arg  
 225                                      230                                      235                                      240  
 40 Ser Ser Val Pro Thr Thr Ser Ile Pro Gly Thr Pro Thr Val Asp Leu  
                                     245                                      250                                      255  
 Gly Thr Ser Gly Thr Pro Val Ser Lys Pro Gly Pro Ser Ala Ala Ser  
 45                                      260                                      265                                      270  
 Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg  
                                     275                                      280                                      285  
 50 Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg Lys Phe Asn Thr Thr  
                                     290                                      295                                      300  
 55 Glu Arg Val Leu Gln Gly Leu Leu Arg Ser Leu Phe Lys Ser Thr Ser

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	305	310	315	320
5	Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu			
		325	330	335
	Lys Asp Gly Thr Ala Thr Gly Val Asp Ala Ile Cys Thr His His Pro			
10		340	345	350
	Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu			
		355	360	365
15	Ser Gln Leu Thr His Asn Ile Thr Glu Leu Gly His Tyr Ala Leu Asp			
		370	375	380
20	Asn Asp Ser Leu Phe Val Asn Gly Phe Thr His Arg Ser Ser Val Ser			
		385	390	395
	Thr Thr Ser Thr Pro Gly Thr Pro Thr Val Tyr Leu Gly Ala Ser Lys			
25		405	410	415
	Thr Pro Ala Ser Ile Phe Gly Pro Ser Ala Ala Ser His Leu Leu Ile			
		420	425	430
30	Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn			
		435	440	445
35	Met Trp Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln			
		450	455	460
	Gly Leu Leu Arg Pro Leu Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr			
40		465	470	475
	Ser Gly Ser Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Glu Ala			
		485	490	495
45	Thr Gly Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Thr Gly Pro			
		500	505	510
	Gly Leu Asp Arg Glu Gln Leu Tyr Leu Glu Leu Ser Gln Leu Thr His			
50		515	520	525
	Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr			
55		530	535	540

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Val Asn Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly  
5 545 550 555 560  
Val Val Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu  
565 570 575  
10 Arg Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile  
580 585 590  
Thr Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg Ser  
15 595 600 605  
Ser Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser  
20 610 615 620  
Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu  
625 630 635 640  
25 Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu  
645 650 655  
Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu  
30 660 665 670  
Asp Lys Asp Ser Leu Tyr Leu Asn Gly Tyr Asn Glu Pro Gly Leu Asp  
675 680 685  
35 Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro Leu  
690 695 700  
40 Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu  
705 710 715 720  
Asn Phe Thr Ile Ser Asn Leu Gln Tyr Ser Pro Asp Met Gly Lys Gly  
45 725 730 735  
Ser Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg  
740 745 750  
50 Pro Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln  
755 760 765  
55 Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp

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	770	775	780
5	Thr Thr Cys Thr Tyr His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile		
	785	790	795 800
	Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln		
10		805	810 815
	Leu Gly Phe Tyr Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr		
		820	825 830
15	Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His		
		835	840 845
	Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr		
20		850	855 860
	Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys		
25		865	870 875 880
	Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr Asn Leu		
		885	890 895
30	Thr Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe Ser Ser Asn		
		900	905 910
	Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn		
35		915	920 925
	Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His		
40		930	935 940
	Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser		
		945	950 955 960
45	Thr Gln His Phe Tyr Pro Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser		
		965	970 975
	Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg		
50		980	985 990
	Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys		
55		995	1000 1005

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Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn  
 5           1010                   1015                   1020  
 Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala  
 1025                   1030                   1035                   1040  
 10 Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr  
                  1045                   1050                   1055  
 Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val  
 15                   1060                   1065                   1070  
 Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn  
 20                   1075                   1080                   1085  
 Ser Asp Leu Pro Phe Trp Ala Val Ile Phe Ile Gly Leu Ala Gly Leu  
                  1090                   1095                   1100  
 25 Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg  
                  1105                   1110                   1115                   1120  
 Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly  
 30                   1125                   1130                   1135  
 Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln  
 35                   1140                   1145  
  
 40 <210> 132  
      <211> 526  
      <212> PRT  
 45 <213> Homo sapiens  
  
 50 <400> 132  
 Met Gly His Leu Ser Ala Pro Leu His Arg Val Arg Val Pro Trp Gln  
      1                   5                   10                   15  
 55 Gly Leu Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr

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	20	25	30
5	Thr Ala Gln Leu Thr Thr Glu Ser Met Pro Phe Asn Val Ala Glu Gly		
	35	40	45
	Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln Gln Leu Phe Gly		
10	50	55	60
	Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Val		
	65	70	75
15	Gly Tyr Ala Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Asn Ser		
	85	90	95
20	Gly Arg Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Val		
	100	105	110
	Thr Gln Asn Asp Thr Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp		
25	115	120	125
	Leu Val Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Pro Glu Leu		
	130	135	140
30	Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys		
	145	150	155
	Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Thr Gln Asp Thr Thr Tyr		
35	165	170	175
	Leu Trp Trp Ile Asn Asn Gln Ser Leu Pro Val Ser Pro Arg Leu Gln		
40	180	185	190
	Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Leu Ser Val Thr Arg Asn		
	195	200	205
45	Asp Thr Gly Pro Tyr Glu Cys Glu Ile Gln Asn Pro Val Ser Ala Asn		
	210	215	220
	Arg Ser Asp Pro Val Thr Leu Asn Val Thr Tyr Gly Pro Asp Thr Pro		
50	225	230	235
	Thr Ile Ser Pro Ser Asp Thr Tyr Tyr Arg Pro Gly Ala Asn Leu Ser		
55	245	250	255

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Leu Ser Cys Tyr Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser Trp Leu  
 5                                   260                                   265                                   270  
 Ile Asn Gly Thr Phe Gln Gln Ser Thr Gln Glu Leu Phe Ile Pro Asn  
                                  275                                   280                                   285  
 10 Ile Thr Val Asn Asn Ser Gly Ser Tyr Thr Cys His Ala Asn Asn Ser  
                                  290                                   295                                   300  
 Val Thr Gly Cys Asn Arg Thr Thr Val Lys Thr Ile Ile Val Thr Glu  
 15 305                                   310                                   315                                   320  
 Leu Ser Pro Val Val Ala Lys Pro Gln Ile Lys Ala Ser Lys Thr Thr  
 20                                   325                                   330                                   335  
 Val Thr Gly Asp Lys Asp Ser Val Asn Leu Thr Cys Ser Thr Asn Asp  
                                  340                                   345                                   350  
 25 Thr Gly Ile Ser Ile Arg Trp Phe Phe Lys Asn Gln Ser Leu Pro Ser  
                                  355                                   360                                   365  
 Ser Glu Arg Met Lys Leu Ser Gln Gly Asn Thr Thr Leu Ser Ile Asn  
 30                                   370                                   375                                   380  
 Pro Val Lys Arg Glu Asp Ala Gly Thr Tyr Trp Cys Glu Val Phe Asn  
 35 385                                   390                                   395                                   400  
 Pro Ile Ser Lys Asn Gln Ser Asp Pro Ile Met Leu Asn Val Asn Tyr  
                                  405                                   410                                   415  
 40 Asn Ala Leu Pro Gln Glu Asn Gly Leu Ser Pro Gly Ala Ile Ala Gly  
                                  420                                   425                                   430  
 Ile Val Ile Gly Val Val Ala Leu Val Ala Leu Ile Ala Val Ala Leu  
 45                                   435                                   440                                   445  
 Ala Cys Phe Leu His Phe Gly Lys Thr Gly Arg Ala Ser Asp Gln Arg  
                                  450                                   455                                   460  
 50 Asp Leu Thr Glu His Lys Pro Ser Val Ser Asn His Thr Gln Asp His  
                                  465                                   470                                   475                                   480  
 55 Ser Asn Asp Pro Pro Asn Lys Met Asn Glu Val Thr Tyr Ser Thr Leu

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	485	490	495
5	Asn Phe Glu Ala Gln Gln Pro Thr Gln Pro Thr Ser Ala Ser Pro Ser		
	500	505	510
	Leu Thr Ala Thr Glu Ile Ile Tyr Ser Glu Val Lys Lys Gln		
10	515	520	525
15	<210> 133		
	<211> 212		
20	<212> PRT		
	<213> Homo sapiens		
25	<400> 133		
	Met Gly Pro Pro Ser Ala Pro Pro His Arg Glu Cys Ile Pro Trp Gln		
	1 5 10 15		
30	Gly Leu Leu Leu Thr Ala Ser Leu Leu Asn Phe Trp Asn Pro Pro Thr		
	20 25 30		
35	Thr Ala Lys Leu Thr Ile Glu Ser Met Pro Leu Ser Val Ala Glu Gly		
	35 40 45		
	Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly		
40	50 55 60		
	Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Ser Leu Ile Val		
	65 70 75 80		
45	Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Ala Ala Tyr Ser		
	85 90 95		
	Gly Arg Glu Thr Ile Tyr Thr Asn Ala Ser Leu Leu Ile Gln Asn Val		
50	100 105 110		
	Thr Gln Asn Asp Ile Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp		
55	115 120 125		



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Leu Val Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Gln Glu Asn  
5                   130                   135                   140  
Ala Pro Gly Leu Pro Val Gly Ala Val Ala Gly Ile Val Thr Gly Val  
145                   150                   155                   160  
10 Leu Val Gly Val Ala Leu Val Ala Ala Leu Val Cys Phe Leu Leu Leu  
                  165                   170                   175  
Ala Lys Thr Gly Arg Pro Trp Ser Leu Pro Gln Leu Cys Leu Leu Asp  
15                   180                   185                   190  
Val Pro Ser Leu His Cys Leu Gly Pro Pro Thr Gln Pro Gln Asp Ser  
20                   195                   200                   205  
Ser Phe His Leu  
                  210  
25  
<210> 134  
30 <211> 244  
<212> PRT  
35 <213> Homo sapiens  
  
<400> 134  
40 Met Gly Pro Pro Ser Ala Ala Pro Arg Gly Gly His Arg Pro Trp Gln  
                  1                   5                   10                   15  
Gly Leu Leu Ile Thr Ala Ser Leu Leu Thr Phe Trp Asp Pro Pro Thr  
45                   20                   25                   30  
Thr Val Gln Phe Thr Ile Glu Ala Leu Pro Ser Ser Ala Ala Glu Gly  
                  35                   40                   45  
50 Lys Asp Val Leu Leu Leu Ala Cys Asn Ile Ser Glu Thr Ile Gln Ala  
                  50                   55                   60  
55 Tyr Tyr Trp His Lys Gly Lys Thr Ala Glu Gly Ser Pro Leu Ile Ala

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65 70 75 80  
 5 Gly Tyr Ile Thr Asp Ile Gln Ala Asn Ile Pro Gly Ala Ala Tyr Ser  
 85 90 95  
 Gly Arg Glu Gln Val Tyr Pro Asn Gly Ser Leu Leu Phe Gln Asn Ile  
 10 100 105 110  
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## 15 Claims

1. A method of diagnosing colon cancer in an individual comprising:

(a) obtaining a serum sample from said individual; and

(b) detecting the presence of TIMP 1 in said sample, wherein the presence of TIMP 1 in said sample is indicative of colon cancer in said individual.

2. The method of claim 1, wherein said step of detecting comprises:

(a) contacting said serum sample with a polypeptide ligand which is capable of binding to TIMP1 under conditions which permit said polypeptide ligand to bind to TIMP1; and

(b) detecting the binding of said polypeptide ligand to TIMP1, wherein detection of binding is indicative of the presence of TIMP1 in said sample.

3. The method of claim 2, wherein said polypeptide ligand is an antibody.

4. The method of claim 2 or claim 3, wherein said polypeptide ligand comprises a detectable label.

5. The method of any one of the preceding claims, wherein said individual is a human.

6. The method of any one of the preceding claims, further comprising detecting at least one other colon cancer specific marker in said sample, wherein the presence of TIMP 1 and said at least one other colon cancer-specific marker is indicative of colon cancer in said individual.

7. The method of claim 6, wherein said colon cancer-specific marker is selected from the group consisting of the nucleic acid molecules of SEQ ID Nos 1, 3, 5-71, the polypeptide molecules of SEQ ID Nos 2, 4, 72-138, CA 19-9, CA 72-4, TF, sTn, Tn, CA 50, CA 549, CA 242, LASA, and Du-PAN 1 - 5.

8. The method of claim 6 or claim 7, wherein said step of detecting comprises:

(a) contacting said serum sample with a first polypeptide ligand which is capable of binding to TIMP1 and a second polypeptide ligand which is capable of binding to said colon cancer-specific marker, under conditions which permit said first and second polypeptide ligands to bind to TIMP 1 and said colon cancer-specific marker, respectively; and

(b) detecting the binding of said first polypeptide ligand to TIMP 1 and said second polypeptide ligand to said colon cancer-specific marker, wherein detection of binding is indicative of the presence of TIMP1 and said colon cancer-specific marker in said sample.

9. The method of claim 8, wherein said first and second polypeptide ligand are each an antibody.

10. The method of claim 8 or claim 9, wherein said first and second polypeptide ligand comprises a detectable label.

11. The method of any one of claims 1 to 10, further comprising the step of detecting the presence of REG1 $\alpha$  in said sample, wherein the presence of REG1 $\alpha$  in said sample is indicative of colon cancer in said individual.

12. A method of diagnosing colon cancer in an individual comprising:

(a) obtaining a serum sample from an individual; and

(b) detecting the presence of a nucleic acid molecule which encodes TIMP1 in said sample, wherein the presence of TIMP1 of said nucleic acid molecule in said sample is indicative of colon cancer in said individual.

13. The method of claim 12, further comprising detecting at least one other nucleic acid molecule which encodes at least one other colon cancer-specific marker in said sample, wherein the presence of said nucleic acid sequence encoding TIMP1 and said nucleic acid sequence encoding said at least one other colon cancer-specific marker is indicative of colon cancer in said individual.

14. The method of claim 12 or claim 13, wherein said colon cancer specific marker is selected from the group consisting of SEQ ID Nos 1, 3, 5-71, the polypeptide molecules of SEQ ID Nos 2, 4, 72-138, CA 19-9, CA 72-4, TF, sTn, Tn, CA 50, CA 549, CA 242, LASA, and Du - PAN 1 - 5.

15. The method of any one of claims 12 to 14, further comprising the step of detecting presence of a nucleic acid molecule which encodes REG1 $\alpha$  in said sample, wherein the presence of REG1 $\alpha$  of said nucleic acid molecule in said sample is indicative of colon cancer in said individual.

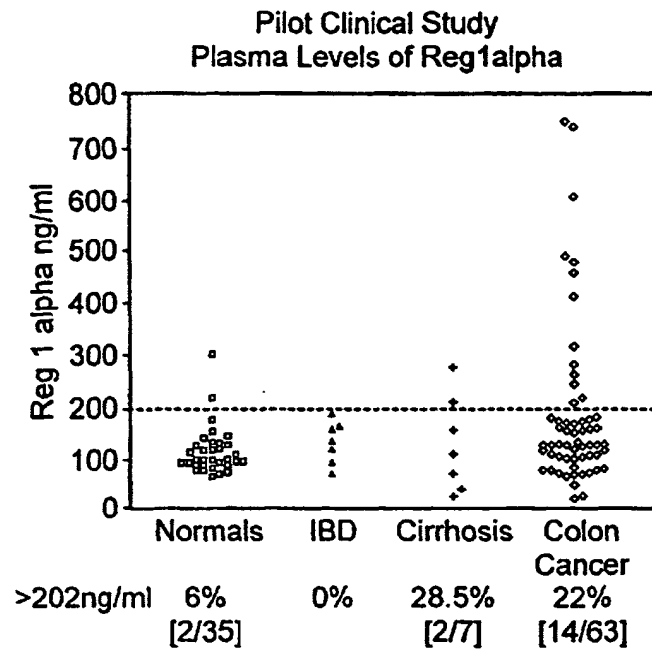


FIG. 1

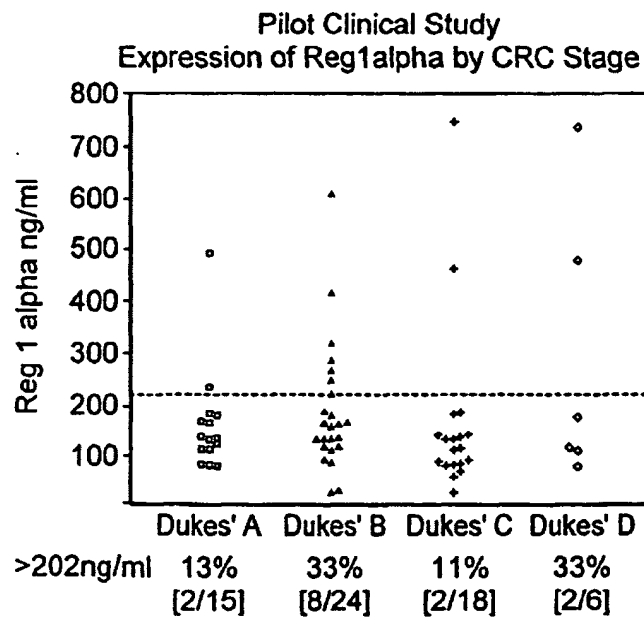


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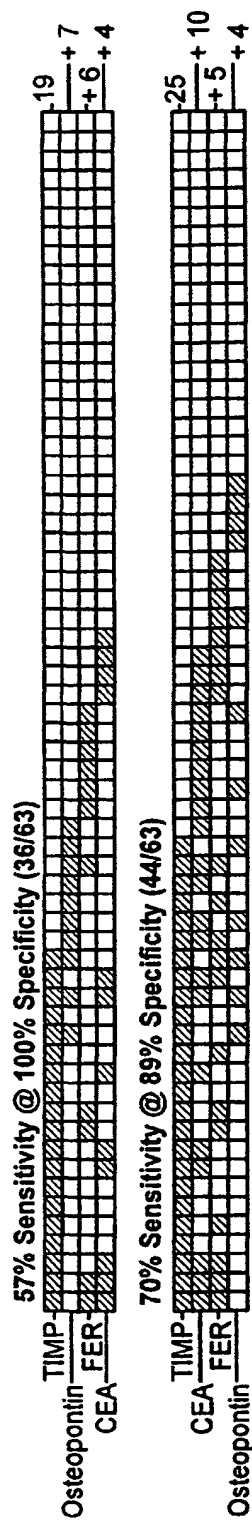
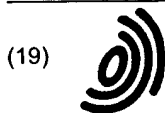


FIG. 3



Europäisches Patentamt  
European Patent Office  
Office européen des brevets



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**31.07.2003 US 491397 P**

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**Rochester, MN 55906 (US)**  
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**179 Queen Victoria Street**  
**London EC4V 4EL (GB)**

(54) **Detection methods using TIMP 1 for colon cancer diagnosis**

(57) The present invention relates to a method for detecting the presence of colorectal cancer in an individual, wherein colorectal cancer is detected by detecting the presence of Reg1 $\alpha$  or TIMP1 nucleic acid or amino acid molecules in a clinical sample obtained from the patient, wherein Reg1 $\alpha$  or TIMP1 expression is indicative of the presence of colorectal cancer. The invention further relates to a method for detecting the presence of

colorectal cancer in an individual, wherein colorectal cancer is detected by detecting the presence of Reg1 $\alpha$  or TIMP1 nucleic acid or amino acid molecules in a clinical sample, in addition to detecting the presence of one or more additional colorectal cancer associated markers.

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European Patent  
Office

# EUROPEAN SEARCH REPORT

Application Number  
EP 03 25 7868

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
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X	WO 02/086085 A (KREBS BARBARA ;KNORR ANDREAS M (DE); KRAFT SABINE (DE); MORPHOSYS) 31 October 2002 (2002-10-31) * abstract; claims *	1-15	
X	WO 01/12781 A (HUMAN GENOME SCIENCES INC ;ROSEN CRAIG A (US); BIRSE CHARLES E (US) 22 February 2001 (2001-02-22) Sequence ID numbers 1 and 14 * abstract; claims *	1-15	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	HOLTON-ANDERSEN M N ET AL: "Measurement of the noncomplexed free fraction of tissue inhibitor of metalloproteinases 1 in plasma by immunoassay" CLINICAL CHEMISTRY, AMERICAN ASSOCIATION FOR CLINICAL CHEMISTRY, WINSTON, US, vol. 48, no. 8, August 2002 (2002-08), pages 1305-1313, XP002959679 ISSN: 0009-9147 * page 1305 - page 1306 *	1-15	G01N
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 26 May 2004	Examiner GONCALVES M L F C
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons &amp; : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03.02 (P04C01)



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## EUROPEAN SEARCH REPORT

Application Number  
EP 03 25 7868

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X	PELLEGRINI P ET AL: "Simultaneous measurement of soluble carcinoembryonic antigen and the tissue inhibitor of metalloproteinase TIMP1 serum levels for use as markers of pre-invasive to invasive colorectal cancer." CANCER IMMUNOLOGY, IMMUNOTHERAPY: CII. GERMANY SEP 2000, vol. 49, no. 7, September 2000 (2000-09), pages 388-394, XP002282255 ISSN: 0340-7004 * page 388 - page 390 *	1-15	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	OKUNO K ET AL: "Gene expression analysis in colorectal cancer using practical DNA array filter." DISEASES OF THE COLON AND RECTUM. UNITED STATES FEB 2001, vol. 44, no. 2, February 2001 (2001-02), pages 295-299, XP009031427 ISSN: 0012-3706 * page 298 - page 299; figures 2,3; table 2 *	1-15	
The present search report has been drawn up for all claims			
Place of search <b>MUNICH</b>		Date of completion of the search <b>26 May 2004</b>	Examiner <b>GONCALVES M L F C</b>
<p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons &amp; : member of the same patent family, corresponding document</p>			

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The members are as contained in the European Patent Office EDP file on  
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26-05-2004

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